



PATENT
Atty. Docket No. P41-9321
SALK1320-3 (088802-1103)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

Evans, *et al.*

Serial No.: 09/526,298

Title: MULTIMERIC FORMS OF
MEMBERS OF THE
STEROID/THYROID
SUPERFAMILY OF RECEPTORS
WITH THE ULTRASPIRACLE
RECEPTOR

Filing Date: March 15, 2000

Group Art Unit: 1635

Examiner: Sean McGarry

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APPEAL BRIEF

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Applicants (herein, "Appellants") submit this Appeal Brief in response to the Final Rejection of claims 14-19 and 35-48. This Appeal Brief is accompanied by the requisite fee set forth in 37 C.F.R. § 1.17(f). If this fee is incorrect or if any additional fees are due in this regard, please charge or credit Deposit Account No. 50-0872 for the appropriate amount.

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Real Party in Interest

The real parties in interest in this appeal is The Salk Institute For Biological Studies, which is the assignee of the present application, and Ligand Pharmaceuticals, Inc., which is the licensee of the present application.

Related Appeals and Interferences

Appellants are not aware of any related appeals or interferences that may have a bearing on the board's decision in the pending appeal.

Status of Claims

On December 21, 2001, Appellants' Notice of Appeal was transmitted by facsimile to the Patent and Trademark Office, appealing the Examiner's Action of August 22, 2001, making final the rejection of claims 14-19 and 35-48. These claims stand finally rejected under 35 U.S.C. § 112, first paragraph. Claims 49-53 have been withdrawn from consideration by the Examiner. The text of claims 14-19 and 35-53 are attached hereto as Appendix A.

Status of Amendments

In an amendment responsive to the Examiner's Action of August 22, 2001, transmitted by facsimile on December 6, 2001, Appellants requested cancellation of claims 49-53. In an Advisory Action dated January 2, 2002, the Examiner indicated that this amendment had been received, but did not indicate whether or not the amendment had been entered.

Summary of The Invention

The present invention relates to methods for modulating the expression of a gene in a subject. According to the claims, the subject contains one or more cells comprising: a gene of interest under the control of a steroid or steroid-like hormone response element; an ultraspiracle receptor; and a receptor that, in the presence of its cognate ligand and the ultraspiracle receptor, binds to the steroid or steroid-like hormone response element. By contacting such cells with the cognate ligand, the expression of the gene of interest can be modulated.

At the time the instant patent application was filed, it was known that steroid and thyroid hormones exert potent metabolic and developmental effects in a diverse group of organisms, including humans. Their action was believed to be mediated via specific binding of a particular hormone with a polypeptide present within target cells, known as a “receptor,” which subsequently binds to a DNA sequence known as a “hormone response element” to control the transcription of genes. *See, e.g.,* specification, page 1, line 17, through page 2, line 21.

Many of these receptors were known to bind to hormone response elements primarily as pairs of identical receptors, referred to as receptor “homodimers.” *See, e.g.,* specification, page 3, lines 15-20. Members of one receptor family – the retinoid X receptor family, were believed to interact with certain types of steroid or steroid-like hormone receptors to form pairs of non-identical receptors, referred to as receptor “heterodimers.” The capability of such receptors to form heterodimers was suggested to provide an elaborate network through which the various

receptors might be capable of controlling the transcription of target genes. *See, e.g.*, specification, page 3, line 32, through page 4, line 21.

The present invention recognized for the first time, *inter alia*, that an insect-derived receptor, known as the “ultraspiracle receptor,” is capable of forming heteromeric receptor forms with certain types of steroid or steroid-like hormone receptors, much like the retinoid X receptor family, with the result that such heteromeric receptors can control the transcription of target genes. *See, e.g.*, specification, page 4, line 25, through page 5, line 1. Because the ultraspiracle receptor is not ordinarily present in non-insect cells (*see, e.g.*, specification, page 6, lines 26-35), the present applicants recognized that its introduction into cells that do not normally contain the ultraspiracle receptor would provide an attractive means of transcriptional control of gene expression, because transcription of the target gene(s) can be limited to only those cells into which the ultraspiracle receptor has been introduced. Additionally, because cells comprising such ultraspiracle-based transcriptional control systems can respond to an external stimulus (*e.g.*, exposure to a hormone), the transcriptional control of gene expression provided by such systems provide a convenient “on” or “off” switch to the artisan.

Thus, the present claims are drawn to methods for modulating the expression of an endogenous gene in a subject containing (i) a DNA construct encoding a gene that is under control of a steroid or steroid-like hormone response element that is not normally present in the cells of the subject; (ii) a receptor that, in the presence of the appropriate ligand and the ultraspiracle receptor, binds to the hormone response element; and (iii) the ultraspiracle receptor;

and administering the appropriate ligand to the subject.

Issues

1. Whether a *prima facie* case of lack of enablement has been established when the Examiner has interpreted claims directed to methods for modulating expression of a gene in a subject to be directed exclusively to “nucleic acid based therapy” despite the fact that this term does not appear in the claims; when the Examiner contends that claims that “read on nucleic acid based therapy” must enable “nucleic acid based therapy;” and when the specification enables methods for practicing the claimed invention by a means that does not require “nucleic acid based therapy” as that term is used by the Examiner.

Grouping of Claims

Claim 14 and 17-19 stand or fall together, claims 15 and 16 stand or fall together, claims 35 and 38-40 stand or fall together, claims 36 and 37 stand or fall together, claims 42 and 45-48 stand or fall together, and claims 43 and 44 stand or fall together.

Specifically, claims 14 and 17-19 relate to methods for modulating expression of a gene by administering a ligand to a subject comprising (i) a DNA construct encoding the gene that is under control of a steroid or steroid-like hormone response element that is not normally present in the cells of the subject; (ii) a receptor that, in the presence of the appropriate ligand and the ultraspiracle receptor, binds to the hormone response element; and (iii) the ultraspiracle receptor;

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claims 15 and 16 relate to methods according to claim 14, in which the receptor not normally present in the cells of the subject, and the ultraspiracle receptor, are encoded by DNA constructs;

claims 35 and 38-40 relate to methods for inducing expression of a gene in a subject comprising (i) a DNA construct encoding a gene that is under control of a steroid or steroid-like hormone response element that is not normally present in the cells of the subject; (ii) DNA encoding a receptor that, in the presence of the appropriate ligand and the ultraspiracle receptor, binds to the hormone response element; (iii) the ultraspiracle receptor; and (iv) an appropriate ligand, by subjecting the subject to conditions suitable to induce expression of the receptor normally present in the cells of the subject;

claims 36 and 37 relate to methods according to claim 35, in which the ultraspiracle receptor is encoded by a DNA construct;

claims 42 and 45-48 relate to methods for inducing expression of a gene in a subject comprising a DNA construct encoding the gene that is under control of a steroid or steroid-like hormone response element that is not normally present in the cells of the subject, by introducing into the subject (i) a receptor that, in the presence of the appropriate ligand and the ultraspiracle receptor, binds to the hormone response element; (ii) the ultraspiracle receptor; and (iii) the appropriate ligand; and

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claims 43 and 44 relate to methods according to claim 42, in which the receptor not normally present in the cells of the subject and the ultraspiracle receptor are encoded by DNA constructs.

Argument

The rejection claims 14-19 and 35-48 for allegedly failing to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, is respectfully submitted to be in error for the following reasons.

Appellants respectfully submit that the Examiner has failed to establish a *prima facie* case of lack of enablement. First, by insisting that the instant claims are “drawn to nucleic acid based therapy” (Paper No. 9, paragraph bridging pages 2 and 3) despite the fact that the phrase “nucleic acid based therapy” does not appear in the claims, the Examiner has interpreted the instant claims improperly by importing limitations into the claims despite plain language in the claims to the contrary. In similar fashion, the Examiner has erroneously asserted that the claims allegedly “involve methods of introducing and expressing exogenous genes and nucleic acid sequences in specific cells in a whole animal” (Paper No. 9, page 3) despite the fact that the claims do not require performing methods in which genes are introduced into specific cells *in vivo*.

Moreover, Appellants respectfully submit that, by insisting that the specification must enable gene therapy in order to meet the enablement standard because the claims “read on” gene therapy (Paper No. 9, pages 4-5), the Examiner has revealed a flawed understanding of the standard by which enablement is measured. This insistence ignores the settled law which

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indicates that the specification need not enable each and every method of practicing the claimed invention. Based on this flawed understanding of how the enablement standard is to be judged, the Examiner's has failed to consider that other means for practicing the claimed invention are sufficient to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. This has led to an erroneous conclusion by the Examiner that the claims are not enabled.

For these reasons, Appellants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn or reversed.

Standard for determining compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph

The standard for determining enablement is whether the specification as filed provides sufficient information to permit one skilled in the art to make and use the claimed invention.

United States v. Telectronics, Inc., 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Moreover, it is not necessary that the specification as filed enable each and every manner for making and using the claimed invention. Instead, in order to satisfy the enablement requirement, the specification need only disclose one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim. *See, e.g., Johns*

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Hopkins Univ. v. CellPro, Inc., 47 USPQ2d 1705, 1917 (Fed. Cir. 1998) (stating that the enablement requirement is met if the description enables any mode of making and using the invention) (emphasis added); *see also*, MPEP §2164.01(b) (failure to disclose other methods by which the claimed invention may be made does not render a claim invalid for lack of enablement).

By insisting that the instant claims are “drawn to nucleic acid based therapy,” the Examiner persists in interpreting the instant claims in a flawed manner

As discussed above, the instant claims relate to methods for modulating gene expression in subjects that contain: a DNA construct encoding an exogenous gene under control of a hormone response element; a receptor that, when bound to ultraspiracle receptor and a ligand, binds to the hormone response element; and ultraspiracle receptor. The Examiner incorrectly interprets this claim language to indicate that the claims “are drawn to nucleic acid therapy” (Paper No. 9, page 3) despite the fact that this phrase never appears in the claims. Based on this extremely narrow interpretation of what the claims are allegedly “drawn to” and therefore what the claims “require” (*see, e.g., Id.*), the Examiner erroneously concludes that, only by enabling “gene therapy” can the specification satisfy 35 U.S.C. §112, first paragraph. *Id.*, pages 3-4.

The Examiner’s flawed interpretation of the claims is highlighted by the Examiner’s discussion in Paper No. 9, page 3, as to why the instant claims allegedly fail to satisfy the enablement requirement (emphasis added):

For example, the instant specification fails to teach one of skill in the art how to integrate the gene construct for the exogenous ultraspiracle receptor to specific

desired cells such that expression would be at a level adequate for inducing the expression of a gene under the appropriate hormone response element. The targeting of specific cells would be required, for example in cases where as applicant contemplates and claims, a method of selectively killing cells and for directing expression of a desired gene in a specific cell type or tissue type.

In fact, in contradiction to the foregoing quoted discussion discussion, the instant claims do not require that a gene construct be integrated into specific cells, or refer to “selectively killing cells” or “expression of a desired gene in a specific cell type or tissue type.” While Appellants disagree that the specification as filed fails to enable the methods to which the Examiner refers, Appellants respectfully submit that the Examiner’s statement, quoted above, is not relevant to the instant claims. Instead, the instant claims require only that a subject contain a DNA construct encoding an exogenous gene under control of a hormone response element; a receptor that, when bound to ultraspircle receptor and a ligand, binds to the hormone response element; and ultraspircle receptor. Such a method could be performed by, for example, inserting each of these elements into cells *in vitro*, *e.g.*, in culture, and then introducing those cells into a subject for various purposes, including therapeutic purposes. *See, e.g.*, specification, page 19, lines 29-35, and page 21, lines 23-28. Such methods are referred to in the art as “*ex vivo*” methods. *See, e.g.*, R.G. Crystal, *Science* 270: 404-410 (1995), Table 2 (describing successful *ex vivo* strategies).

Such methods are fully capable of providing each and every element of the instant claims without the need to perform “gene therapy” as that term is used by the Examiner. Thus, contrary to the Examiner’s assertions, the instant claims are not directed to nucleic acid therapy *per se*; nor are the claims directed to introducing genes into specific cells in a whole animal. Instead, the

instant claims are drawn to any of a number of possible applications, based on the realization by Appellants that gene expression can be modulated using a receptor that, in the presence of the ultraspiracle receptor and a ligand, binds to hormone response elements.

Accordingly, Appellants respectfully submit that the Examiner's interpretation of the claims is improper and overly narrow because the Examiner includes elements that are not present in the claims. *See, e.g., Johnson Worldwide Associates, Inc. v. Zebco Corp.*, 50 USPQ2d 1607, 1610 (Fed. Cir. 1999) ("[T]here must be a textual reference in the actual language of the claim with which to associate a proffered claim construction."); *Id.* ("If we once begin to include elements not mentioned in the claim in order to limit such a claim..., we should never know when to stop."); quoting *McCarty v. Lehigh Valley R.R.*, 160 U.S. 110, 116 (1895)); *see also*, MPEP §2111.01 (importing limitations not present in the claims is not a reasonable claim interpretation). Because the enablement rejection is based squarely on this improper interpretation, the Examiner has failed to establish a *prima facie* case of lack of enablement of the instantly claimed invention.

By insisting that, because the instant claims "read on nucleic acid based therapy," nucleic acid therapy must be enabled, the Examiner reveals a flawed understanding of the enablement standard

Additionally, Appellants respectfully submit that, by insisting that methods the Examiner variously refers to as "nucleic acid based therapy" (Paper No. 12, page 2) and "gene therapy" (Paper No. 9, pages 4-5) must be enabled in order to meet the enablement standard, because the

instant claims allegedly “read on” such methods, the Examiner demonstrates a flawed understanding of the standard by which enablement is properly measured.

As stated by the Court of Appeals for the Federal Circuit in the *CellPro* decision referred to above, it is not necessary that the specification enable each and every manner for making and using the claimed invention. Rather, so long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, the enablement requirement of 35 U.S.C. §112, first paragraph is satisfied. Thus, in contradiction to the Examiner’s contention in Paper No. 12, whether or not the instant claims “read on” one particular method by which the claimed invention may be practiced is not probative of whether or not the claims comply with the enablement requirement, when the Examiner has ignored all other methods by which the claimed invention may be practiced.

Accordingly, Appellants respectfully submit that, by focusing on “gene therapy” to the exclusion of all other methods by which the instant claims may be practiced, the Examiner has failed to establish a *prima facie* case of lack of enablement of the instantly claimed invention.

When properly interpreted and when judged by the proper standard, it becomes clear that the instant claims satisfy the enablement requirement

When the claims are properly interpreted, it is clear that the instant claims do meet the enablement standard of 35 U.S.C. § 112, first paragraph, because the skilled artisan could readily make and use the claimed invention without undue experimentation.

The instant specification provides extensive guidance for carrying out methods for modulating genes in cells, and particularly in cultured cells. Indeed, the Examiner concedes that

the methods described in the instant specification for modulating gene expression in cultured cells do meet the enablement standards of 35 U.S.C. § 112. *See*, Paper No. 9, page 2. Based on the knowledge of *ex vivo* strategies within the art, the skilled artisan would clearly understand and readily acknowledge that methods useful for manipulating gene expression in cultured cells may be employed to manipulate gene expression in subjects, as contemplated by the instant claims. *See, e.g.*, specification, page 19, lines 29-35, and page 21, lines 23-28; *see also*, R.G. Crystal, *Science* 270: 404-410 (1995), Table 2 (describing successful *ex vivo* strategies).

Appellants respectfully submit that the Examiner's attempts to minimize the understanding within the art of such *ex vivo* methods by professing an ignorance both the teachings of the instant specification and the high level of skill in the art are misplaced. *See, e.g.*, Paper No. 9, page 6 ("[w]hat cell types would one use in *ex vivo* applications, how would one make them such that ligands delivered *in vivo* would enter the *ex vivo* delivered cells such that a modulation could be established...?"). It is axiomatic that enablement must be judged from the point of view of the skilled artisan, and not from the point of view of one apparently unfamiliar with the knowledge generally available in that art. In fact, methods for introducing DNA constructs into subjects, whether *in vivo* or *ex vivo*, were well known to the skilled artisan at the time the instant application was filed. *See, e.g.*, R.G. Crystal, page 405, right column ("Although gene transfer has not been demonstrated in all recipients, most studies have shown that genes can be transferred... whether the strategy is *ex vivo* or *in vivo*..., with successful human gene transfer having been demonstrated in 28 *ex vivo* and 10 *in vivo* studies."). Appropriately, the choice of

cell type for use in such methods in the instant claims is left to the discretion of the skilled artisan.

Furthermore, the Examiner's contention that "Applicant has not demonstrated that such [nucleic acid] constructs [for use in practicing the claimed invention] were available at the time of the invention" (Paper No. 12, page 2) is clearly at odds with the Examiner's admission that the methods described in the instant specification for modulating gene expression in cultured cells meet the enablement standards of 35 U.S.C. § 112. *See*, Paper No. 9, page 2. The skilled artisan would readily acknowledge the direct applicability of these methods to the *ex vivo* studies referred to by the Crystal publication. Indeed, the Examiner's contention only serves to further emphasize the fact that the Examiner has improperly focused exclusively upon a need to enable "gene therapy," as the examiner defines that term, to the exclusion of all other methods by which the instant claims may be practiced.

With regard to how one might deliver ligands that would enter cells, the skilled artisan is well aware, and the instant specification teaches, that steroid hormones naturally exert their biological effects by entering cells and binding to hormone receptors. Thus, to argue that, somehow, undue experimentation would be required to obtain entry of an appropriate ligand unreasonably ignores the well established biology of such hormones. Furthermore, with regard to how modulation of a gene could be established, Appellants respectfully submit that this is, in fact, a key feature of, and is extensively described by, the instant specification. Moreover, as discussed above, the Examiner concedes that the exemplary methods described in the instant

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specification for modulating gene expression in cultured cells meet the enablement standards of 35 U.S.C. § 112. Paper No. 9, page 2. Thus, the skilled artisan need only follow the teachings of the instant specification to establish modulation of a gene.

Appellants respectfully submit that, whether or not the Examiner is correct that “[n]ucleic acid based therapy is an unpredictable art and one of skill in the art is in need of specific guidance for any specif[ic] gene therapy” (Paper No. 9, page 4), this is irrelevant to the instant claims. The present invention is not directed to “any specific gene therapy,” but rather to methods for modulating expression of exogenous genes. The skilled artisan can readily perform the instantly claimed methods using only well known methods and with only a level of experimentation typically engaged in by the artisan. *See*, MPEP § 2164.01 (the fact that experimentation may be complex does not make it undue if the art typically engages in such experimentation). 35 U.S.C. §112 demands no more.

Therefore, because the claims meet the enablement standard of 35 U.S.C. §112, first paragraph, Appellants respectfully request that the rejection be withdrawn or reversed.

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Conclusion

For the reasons discussed above, the instant claims are in condition for allowance, and Appellants respectfully request that the rejections be withdrawn or reversed, and that the rejected claims, together with those claims that the Examiner has indicated are in allowable form, be allowed to issue.

Respectfully submitted,
FOLEY & LARDNER

Dated: 3/21/02

By: Stephen E. Reiter
Stephen E. Reiter
Registration No. 31,192
Telephone: (858) 847-6711
Facsimile: (858) 792-6773

FOLEY & LARDNER
P. O. Box 80278
San Diego, CA 92138-0278

Appendix A: Text of the Claims Involved in the Appeal

14. A method for modulating the expression of an exogenous gene in a subject containing:

- (i) a DNA construct encoding said exogenous gene under the control of a steroid or steroid-like hormone response element; wherein said response element is not normally present in the cells of said subject,
- (ii) a receptor which is not normally present in the cells of said subject, wherein said receptor, in the presence of its associated ligand and the ultraspiracle receptor, binds to said steroid or steroid-like hormone response element, and
- (iii) ultraspiracle receptor;

 said method comprising administering to said subject an effective amount of said associated ligand; wherein said ligand is not normally present in the cells of said subject; and wherein said ligand is not toxic to said subject.

15. A method according to Claim 14 wherein said receptor not normally present in the cells of the subject and said ultraspiracle receptor are provided to said subject by DNA construct(s) encoding said receptors.

16. A method according to Claim 15 wherein said receptors are expressed under the control of a tissue specific promoter.

17. A method according to claim 14 wherein said exogenous gene is selected from the group consisting of a gene naturally contained in the genome of said subject, and a gene not naturally contained in the genome of said subject.

18. A method according to Claim 17 wherein said wild type genes are selected from genes which encode gene products:

the substantial absence of which leads to the occurrence of a non-normal state in said subject; or

a substantial excess of which leads to the occurrence of a non-normal state in said subject.

19. A method according to Claim 17 wherein said therapeutic genes are selected from those which encode gene products:

which are toxic to the cells in which they are expressed; or

which impart a beneficial property to said subject.

35. A method of inducing the expression of an exogenous gene in a subject containing:

- a) a DNA construct encoding an exogenous gene product under the control of a hormone response element; wherein said response element is not normally present in the cells of said subject,
- b) DNA encoding a receptor which is not normally present in the cells of said subject, under the control of an inducible promoter; wherein said receptor, in the presence of its associated ligand and the ultraspirelre receptor, binds to said hormone response element,
- c) ultraspirelre receptor, and
- d) the associated ligand for said receptor which is not normally present in the cells of said subject,

said method comprising subjecting a subject to conditions suitable to induce expression of said receptor which is not normally in the cells of said subject.

36. A method according to claim 35, wherein said ultraspiracle receptor is provided to said subject by a DNA construct encoding said ultraspiracle receptor.

37. A method according to claim 36, wherein said receptors are expressed under the control of a tissue-specific promoter.

38. A method according to claim 35, wherein said ultraspiracle receptor is substantially the same as that set forth in amino acids 1-513 of SEQ ID NO:2.

39. A method according to claim 35, wherein said exogenous genes are wild type genes or therapeutic genes.

40. A method according to claim 39, wherein said wild type genes encode gene products:

(a) the substantial absence of which leads to the occurrence of a non-normal state in said subject, or

(b) a substantial excess of which leads to the occurrence of a non-normal state in said subject.

41. A method according to claim 39, wherein said therapeutic genes encode gene products:

(a) which are toxic to the cells in which they are expressed, or

(b) which impart a beneficial property to said subject.

42. A method of inducing expression of an exogenous gene product in a subject containing a DNA construct encoding said product under the control of a hormone response element; wherein said response element is not normally present in the cells of said subject, said method comprising introducing into said subject:

(a) a receptor which is not normally present in the cells of said subject;

wherein said receptor, in combination with its associated ligand and ultraspiracle receptor, binds to said hormone response element, activating transcription therefrom,

- (b) the ultraspiracle receptor, and
- (c) the associated ligand for said receptor.

43. A method according to claim 42, wherein said receptor not normally present in the cells of said subject and said ultraspiracle receptor are provided to said subject by DNA construct(s) encoding said receptors.

44. A method according to claim 43, wherein said receptors are expressed under the control of a tissue-specific promoter.

45. A method according to claim 42, wherein said ultraspiracle receptor is substantially the same as that set forth in amino acids 1-513 of SEQ ID NO:2.

46. A method according to claim 42, wherein said exogenous genes are wild type genes or therapeutic genes.

47. A method according to claim 46, wherein said wild type genes encode gene products:

- (a) the substantial absence of which leads to the occurrence of a non-normal state in said subject, or
- (b) a substantial excess of which leads to the occurrence of a non-normal state in said subject.

48. A method according to claim 46, wherein said therapeutic genes encode gene products:

- (a) which are toxic to the cells in which they are expressed, or
- (b) which impart a beneficial property to said subject.

49. A method to distinguish the physiological effect of a first hormone receptor in a host from other hormone receptors in said host which respond to the same ligand, said method comprising:

(a) replacing the ligand binding domain of said first receptor with a ligand binding domain from an exogenous receptor to produce a chimeric receptor maintained under the control of a tissue specific promoter;

wherein said exogenous receptor and the ligand to which the exogenous receptor responds are not normally present in said host; and wherein said exogenous receptor, in the presence of its associated ligand, binds to a hormone response element, thereby activating said response element, and thereafter

(b) monitoring the production of product(s) whose expression is controlled by said first hormone receptor when said host is exposed to ultraspiracle receptor and ligand to which said exogenous receptor responds.

50. A method to render mammalian hormone receptor(s) uniquely responsive to a ligand not endogenous to host(s) in which said receptor is normally found, said method comprising:

(a) replacing the ligand binding domain of said receptor with a ligand binding domain from a second receptor;

wherein said second receptor is not normally present in said host; and wherein the ligand to which the second receptor responds is not normally present in said host.

51. A method according to claim 50, wherein said second receptor is ultraspiracle receptor.

52. A method according to claim 50, wherein said ultraspiracle receptor has an amino acid sequence that is substantially the same as that set forth in amino acids 1-513 of SEQ ID NO:2.

53. A method to determine the ligand(s) to which orphan receptor(s) responds, said method comprising:

monitoring a host cell containing a reporter construct and a hybrid receptor for expression of product(s) of said reporter construct upon contacting said cell with potential ligands for said orphan receptor and the ultraspiracle receptor; wherein said reporter construct comprises a gene encoding a reporter molecule, operatively linked for transcription to a steroid or steroid-like hormone response element; wherein said response element is not normally present in the cells of said host; wherein said hybrid receptor comprises:

the N-terminal domain and DNA binding domain of a member of the steroid/thyroid superfamily of receptors, wherein said member is not normally present in the host cells, and wherein said member, in the presence of its associated ligand and ultraspiracle receptor, binds said response element, activating transcription therefrom, and

the ligand binding domain of said orphan receptor.

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v.
Teletronics Inc.

Court of Appeals, Federal Circuit

Nos. 87-1445, -1446

Decided September 22, 1988

United States Patents Quarterly Headnotes

PATENTS

[1] Patent construction -- Claims -- Broad or narrow (§ 125.1303)

Federal district court erred in interpreting claim for bone growth stimulator device by limiting claim to non-implanted anodes and excluding anodes implanted adjacent to bone and by basing interpretation on claim language which cautions against formation of "fibrous tissue" around anode, since such language is not determinative of anode placement.

PATENTS

[2] Patent construction -- Claims -- Broad or narrow (§ 125.1303)

Doctrine of claim differentiation presumes difference in meaning and scope when different words or phrases are used in separate claims, and thus federal district court erroneously construed claim of bone healing invention so that its limitations are same as dependent claim.

PATENTS

[3] Infringement -- Literal infringement (§ 120.05)

Determination that claims for patented bone growth stimulator device, as properly construed, encompass both skin anode and implanted anode warrants finding of literal infringement by defendant's device, in view of defendant's admission that literal infringement is avoided only if patented device's claims are construed to be limited to skin anode.

PATENTS

[4] Patentability/Validity -- Adequacy of disclosure (§ 115.12)

Patent infringement defendant which seeks to prove invalidity based upon non- enablement must show facts, supported by clear and convincing evidence, demonstrating that patent was not enabling, and federal district court findings that claims for patented bone growth stimulator device are not limited to specific metal/current combination, and that determination of optimal electrical current for materials other than stainless steel would require dose response study and would involve "undue amount of experimentation," are insufficient to establish clear and convincing proof of invalidity, since time and cost of such studies do not, standing alone, show experimentation to be excessive.

PATENTS

Particular patents -- General and mechanical -- Medical healing device

3,842,841, Brighton, Friedenberg, and Redka, constant current power pack for expediting healing of bone fracture and bone defects in living beings, including means of internal implant, and method of using device, valid and infringed.

*1217 Appeal from the U.S. District Court for the District of Colorado, Matsch, J; 3 USPQ2d 1571.*1218

Patent infringement action brought by U.S. and Zimmer Inc., as involuntary plaintiff, against Teletronics Inc. and BGS Medical Inc. From federal district court's judgment holding that defendants did not infringe, that patent is not invalid under 35 USC 112, and holding that defendant Teletronics is not entitled to attorney's fees, parties cross-appeal. Affirmed in part and reversed in part.

John Fargo (Richard K. Willard, assistant attorney general and Vito J. DiPietro, with him on brief), Department of Justice, for plaintiff/appellant.

Michael I. Rackman, of Gottlieb, Rackman & Reisman, New York, N.Y. (Barry A. Cooper and Jeffrey M. Kaden, New York, and William C. Nealon, Suffield, Conn., with him on brief), for defendants/counterclaim-plaintiffs/cross-appellants.

Before Newman, Archer, and Mayer, circuit judges.

Archer, J.

The United States of America (government) appeals the judgment of the United States District Court for the District of Colorado in United States v. Telectronics, Inc., 658 F.Supp. 579, 3 USPQ2d 1571 (D. Colo. 1987), holding that Telectronics, Inc. and BGS Medical, Inc. (Telectronics) do not infringe U.S. Patent No. 3,842,841 ('841). Telectronics cross-appeals the determinations that the '841 patent is not invalid under 35 U.S.C. § 112 (1982) and that Telectronics is not entitled to attorney fees under 35 U.S.C. § 285 (1982). [FN1] We reverse the district court's holding that the '841 patent is not infringed by Telectronics. The determinations that the patent is not invalid under section 112 and that Telectronics is not entitled to attorney fees are affirmed.

Background

The '841 patent issued to Carl T. Brighton, et al. and was assigned to the United States. The patent resulted from work under contract between the Office of Naval Research and the University of Pennsylvania, where the inventors were employed. 658 F.Supp. at 581, 3 USPQ2d at 1571. The '841 patent is directed to a bone growth stimulator device for speeding the healing of fractures and other bone defects. The accused devices of Telectronics are marketed under the name OSTEOSTIM and include Model 2000 and earlier models S-12, HS-12 and XM-12. Zimmer, Inc. (Zimmer), a licensee of the government under the '841 patent, also markets a bone growth stimulator which the district court found to be "quite similar to the preferred embodiment of the invention shown in the patent." 658 F.Supp. at 581, 3 USPQ2d at 1571.

Normally bone fractures heal naturally as a result of the body's own reparative process. Approximately five percent of the time, however, natural healing does not occur and bone grafting is conventionally employed to attempt to stimulate further reparative growth. 658 F.Supp. at 581-82, 3 USPQ2d at 1572.

Bone growth stimulators are particularly useful in the treatment of fractures normally requiring grafting. The success rate is at least as great as with grafting and the procedure results in less discomfort to the patient. 658 F.Supp. at 582, 3 USPQ2d at 1572. Bone

growth stimulators expedite the healing of a fracture or bone defect by passing a low level constant direct current to the site of the fracture via a cathode placed internally at the site of the fracture. Id. The placement of the circuit-completing anode is at issue in this case.

The claim of the '841 patent at issue reads:

1. A system for expediting the healing of bone fractures and bone defects in a living being comprising:

constant current source means for providing a constant value of current despite changes in load;

means for connecting said constant current means to the living being, such connection acting to produce current flow into said fracture or defect,

said connecting means including further means for application internally of said living being at the fracture or defect site,

said constant current being a selected value within a predetermined microampere range so as to promote bone formation at the fracture or bone defect site and avoid fibrous tissue formation in other areas of the living being.

In describing the operation of the patented invention and the accused devices, the district court stated that

[w]hen using the product of either party, the cathode (negative terminal) is placed in the defect site. The Zimmer cathode is made of stainless steel, the material described in the patent. The OSTEOSTIM cathode is made of titanium. The major *1219 difference between the products of the parties pertains to the anode (positive terminal). As disclosed in the patent drawing and accompanying description, and as marketed by Zimmer, the anode is placed on the skin of the patient. So is the power pack (current source) itself. The only internal element [in Zimmer] is the cathode -- a pin which is inserted through the skin into the defect site. This technique avoids the need for surgery; after several months of treatment, the cathode pin is simply pulled out. The OSTEOSTIM device, on the other hand, is completely implanted, an embodiment which while not shown in the patent drawing is nevertheless described. The power pack and the anode of the OSTEOSTIM are

placed in soft tissue near the bone. The original OSTEOSTIM S-12 had a power pack from which two wires extended, the wires terminating respectively at a titanium cathode for placement in the defect site, and a platinum anode for placement in the soft tissue. In all of the later models, including the OSTEOSTIM-2000, the anode wire was omitted. The anode is the case itself -- titanium with a patch of platinum.

658 F.Supp. at 582, 3 USPQ2d at 1572.

Because the Electronics devices have an implanted anode, the district court stated that "the critical question in the case is whether the language of claim 1 (and with it, the dependent claims) is limited to a skin anode." 658 F.Supp. at 583, 3 USPQ2d at 1573. Electronics contended before the district court that "an internal anode could not come within the literal language of claim 1 because fibrous tissue formation inevitably results from such an implant." *Id.* In finding no literal infringement, the district court held with respect to the accused device that

fibrous tissue formation could not be avoided in the dictionary sense of "keep away from" or "stay clear of".

The claim limitation directed to the avoidance of fibrous tissue means what it plainly says. Accordingly, there is no literal infringement because in the context of the patent, even minimal fibrous tissue formation is not its avoidance. *Id.*

The district court also held that the '841 patent was not infringed under the doctrine of equivalents on the basis that the prosecution history established that the patentees, in responding to rejections by the examiner, repeatedly represented that the invention was limited to a surface or skin anode. After examining the prosecution history in detail, the district court stated: "[i]t is clear from the file history that what convinced the Examiner to allow the claims over the prior art was the argument that a skin anode was used in the invention." 658 F.Supp. at 587, 3 USPQ2d at 1576.

On appeal, the government contends that the district court in its literal infringement analysis erred as a matter of law in its claim interpretation. According to the government, the claim limitation read as a whole requires the constant current supply to be controlled in a manner to minimize the amount of fibrous tissue formed. Electronics counters that the district court

properly interpreted the claim phrase "avoid fibrous tissue formation" and the prosecution history to find that the claim is limited to the use of a skin anode.

OPINION

1. Claim Interpretation

A. Analysis of literal infringement involves two inquiries: first the claims must be properly construed to determine their scope and then it must be determined whether the properly interpreted claims encompass the accused structure. ZMI Corp. v. Cardiac Resuscitator Corp., 844 F.2d 1576, 1578, 6 USPQ2d 1557, 1559 (Fed. Cir. 1988). Claim construction is reviewed as a matter of law. However, interpretation of a claim may depend on evidentiary material about which there is a factual dispute, requiring resolution of factual issues as a basis for interpretation of the claim. Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1054, 5 USPQ2d 1434, 1441 (Fed. Cir. 1988). In interpreting claims resort should be made to the claims at issue, the specification, and the prosecution history. Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 867, 228 USPQ 90, 93 (Fed. Cir. 1985). The question of literal infringement is a factual inquiry and is reviewed on a clearly erroneous standard. Loctite Corp., 781 F.2d at 866, 228 USPQ at 93.

B. The district court interpreted the phrase "avoid fibrous tissue formation" as precluding the use of an implanted anode, and thus limiting the claim to a surface or skin anode. To the court, the word "avoid" based on its dictionary definition meant that there could be no fibrous tissue. Because an implanted anode inevitably resulted in some fibrous tissue, the court determined that this placement of the anode was not covered by the claim language.

The government argues that the district court erred in its interpretation because the phrase at issue was not read in context. It contends that the claim language read as a whole only requires that there be avoidance *1220 or minimization of fibrous tissue formation by controlling or selecting the current. Thus, any fibrous tissue that may result from the implantation of the anode is immaterial.

[1] We agree that the district court erred in its interpretation of the limitation of claim 1 and in its conclusion that such language is determinative of the anode placement. In the claim, constant current is a "selected value . . . so as to promote bone

formation . . . and avoid fibrous tissue formation in other areas." Nothing in this language relates to fibrous tissue that may be formed from implantation of an anode. The plain meaning of the disputed language is only that current related fibrous tissue formation is to be avoided.

In considering other sources for interpretation of claims, we note that the specification supports the plain meaning of the clause at issue. See Autogiro Co. of America v. United States, 384 F.2d 391, 397, 155 USPQ 697, 702-03 (Ct. Cl. 1967) ("[p]atent law allows the inventor to be his own lexicographer. . . . [t]he specification aids in ascertaining the scope and meaning of the language employed in the claims inasmuch as words must be used in the same way in both the claims and the specification.") The specification makes no mention of whether a skin anode or an implanted anode may cause or deter the formation of fibrous tissue. There is, however, a discussion of the increase or decrease in fibrous tissue that is formed with varying currents. Further, we find nothing in the prosecution history that would indicate that fibrous tissue resulting from implantation of an electrode was at issue or was intended to be covered by the claim language.

The claim language relied on by the district court is, therefore, not determinative of anode placement and does not require that claim 1 be limited to a surface or skin anode.

C. Claim 1 recites a "means for connecting said constant current means to the living being, such connection acting to produce current flow into said fracture or defect." Since this recitation is in the "means plus function" format permitted by 35 U.S.C. § 112, P6, it must be interpreted to cover the structure disclosed in the specification and the equivalents thereof. See D.M.I. Inc. v. Deere & Co., 755 F.2d 1570, 1575, 225 USPQ 236, 239 (Fed. Cir. 1985).

"In construing a 'means plus function' claim, as also other types of claims, a number of factors may be considered, including the language of the claim, the patent specification, the prosecution history of the patent, other claims in the patent, and expert testimony [citations omitted]. Once such factors are weighed, the scope of the 'means' claim may be determined." Palumbo v. Don-Joy Co., 762 F.2d 969, 975, 226 USPQ 5, 8 (Fed. Cir. 1985); see also Moeller v. Ionetics Inc., 794 F.2d 653, 656, 229 USPQ 992, 994 (Fed. Cir. 1986) (resort to extrinsic evidence, such as the prosecution history, is necessary to interpret disputed claims); SSIH Equip.

S.A. v. U.S. Int'l Trade Comm'n, 718 F.2d 365, 376, 218 USPQ 678, 688 (Fed. Cir. 1983) (the prosecution history is always relevant to proper claim interpretation). "[T]he prosecution history (or file wrapper) limits the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance." Standard Oil Co. v. American Cyanamid Co., 774 F.2d 448, 452, 227 USPQ 293, 296 (Fed. Cir. 1985); see also McGill Inc. v. John Zink Co., 736 F.2d 666, 673, 221 USPQ 944, 949 (Fed. Cir.), cert. denied, 469 U.S. 1037 (1984).

The district court found that both implanted and surface anodes are disclosed in the specification of the '841 patent. The specification provides: "[a]lthough the cathode must be placed in the fracture . . . the anode, though described as preferably being placed on the remote side of the site from the cathode, may be placed anywhere so long as it completes a circuit with the cathode." Elsewhere the specification provides that "[i]f the anode is to be implanted, it . . . is bared of its cover." Thus, unless other relevant claim interpretation factors clearly require a different construction, the plain language of claim 1 and the specification cover an implanted anode as well as a skin or surface anode.

In its claim construction and literal infringement analysis, the district court did not consider the prosecution history but concluded for the reasons indicated in I.A., *supra*, that a surface anode was required. The prosecution history, however, was extensively discussed in the court's consideration of the doctrine of equivalents.

Prior to allowance, the applicants communicated with the examiner six times. These communications are referred to as "A" through "F" in the district court's opinion and herein. The district court concluded that because of the prosecution history appellant is "prevented from construing its claims to include an internal anode." 658 F.Supp. at 587, 3 USPQ2d at 1577. We disagree.

The district court first relied on Amendments B and C. In the former, applicants inserted the limitation "only one of said connecting means applied to the skin surface of the living being" for the purpose of attempting*1221 to overcome a prior art rejection. This amendment was accompanied by remarks to the same effect. In Amendment C, this limitation was argued to be a distinguishing feature of the invention. Applicants' attempts to distinguish over the prior art in this fashion were unsuccessful, and the claims

were later amended to remove this recitation. The arguments emphasizing the use of a skin electrode, which were made at the time the application claims explicitly contained such a limitation, cannot furnish a basis for restricting issued claim 1, which lacks any such limitation. See Smith v. Snow, 294 U.S. 1, 16 (1935) ("It is of no moment that in the course of the proceedings in the Patent Office the rejection of narrow claims was followed by the allowance of the broader Claim 1."); Kistler Instrumente AG v. United States, 628 F.2d 1303, 1308, 211 USPQ 920 (Ct. Cl. 1980) (aff'g and adopting 203 USPQ 511, 516) (courts are not permitted to read "back into the claims limitations which were originally there and were removed during prosecution of the application through the Patent Office.")

In Amendment D a claim which ultimately issued as independent claim 1 was submitted for the first time. In holding claim 1 should be limited to a skin anode, the district court relied on Amendments E and F which contained arguments relative to a skin anode and which were held by the district court to be in support of the claims that finally issued. [FN2] From Amendment F the district court quoted the following language:

Applicants take strong exception to [the examiner's] analysis of the [Friedenberg-Kohanim article]. Nowhere in this article is there either stated or suggested that one of the electrodes need simply be applied to the surface and the other introduced into the fracture site.

These remarks were submitted to correct the examiner's characterization of a prior art reference (an article written by one of the co-inventors of the patented invention). The examiner's characterization of the reference was made in rejecting claims, at least some of which included an explicit recitation of a surface anode. Thus, these remarks are of little significance.

The district court also noted the following argument in Amendment F:

Applicants throughout the prosecution of this case have repeatedly attempted to convey to the Examiner the important differences between their technique where only one of the electrodes need pierce the skin and enter the fracture site and the other prior art arrangements where two electrodes have to pierce the skin and then fit into prescribed locations formed in the bone structure under study. (Emphasis added.)

The quoted language does not mean that one electrode must remain on the surface of the skin. Rather, as applicants argue, it means that both of their electrodes do not have to be placed in the bone structure itself. The district court erred in construing the phrase "only one of the electrodes need pierce the skin" to mean that the other electrode must remain on the surface. This phrase, when read in conjunction with the words that follow -- "and enter the fracture site" -- only serves to distinguish prior art where both electrodes were placed in the bone structure. [FN3] The entire emphasis of the prior art article was that the electrodes were placed in the bone for the purpose of attempting to lengthen the bone. The article was not concerned with the healing of fractures or bone defects. In the healing of fractures, it is not necessary (or desirable) to place both electrodes in the bone.

[2] D. "There is presumed to be a difference in meaning and scope when different words or phrases are used in separate claims. To the extent that the absence of such difference in meaning and scope would make a claim superfluous, the doctrine of claim differentiation states the presumption that the difference between claims is significant." Tandon Corp. v. United States Int'l Trade Comm'n, 831 F.2d 1017, 1023, 4 USPQ2d 1283, 1288 (Fed. Cir. 1987). "Where some claims are broad and others narrow, the narrow claim limitations cannot be read into the broad whether to avoid invalidity or to escape infringement. Uniroyal, Inc., 837 F.2d at 1054-55, 5 USPQ2d at 1441 (quoting D.M.I., Inc. v. Deere & Co., 755 F.2d at 1574, 225 USPQ at 239).

In this case the district court erroneously construed claim 1 so that its limitations are *1222 the same as dependent claim 2. Claim 2 reads in its entirety: "The system as defined in claim 1 wherein said connecting means includes means for external application to the skin surface, the internal means being a cathodic electrode, the external means being an anodic electrode." The doctrine of claim differentiation, therefore, counsels against limiting claim 1 to the use of a skin anode. See D.M.I., Inc., 755 F.2d at 1574, 225 USPQ at 239.

E. On the basis of the above analysis, we conclude that the district court erred as a matter of law in its interpretation of claim 1 of the '841 patent. Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1569, 219 USPQ 1137, 1140 (Fed. Cir. 1983).

The ordinary and accustomed meaning of claim 1 is

that the current should be applied so as to avoid the formation of fibrous tissue. In support of this means plus function claim, the specification of the '841 patent disclosed both an implanted and a surface anode structure. The other claims, the specification and the prosecution history do not require a narrower construction. Thus, the district court erred in limiting claim 1 to the use of a skin anode.

II. Literal Infringement

The question of literal infringement is a factual inquiry. Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d at 1054, 5 USPQ2d at 1441. Literal infringement requires that every limitation of the patent claim must be found in the accused device. Mannesmann Demag Corp. v. Engineered Metal Prods. Co., 793 F.2d 1279, 1282, 230 USPQ 45, 46 (Fed. Cir. 1986). In this case, the findings of the district court establish literal infringement and, thus, there is no need to remand for a determination of the factual question of infringement under properly interpreted claims.

[3] The district court stated in its opinion that:

The defendant's denial of infringement in this case is based solely on the defendants' anode and case being used internally. Accordingly the critical question in the case is whether the language of claim 1 (and with it the dependent claims) is limited to a skin anode.

As we have held in I., *supra*, the properly construed claims encompass both a skin anode and an implanted anode. The district court erroneously limited the claims of the '841 patent to a surface anode. Accordingly, on the position of Teletronics as stated by the district court, literal infringement is established.

The government also challenges the district court's finding of no infringement under the doctrine of equivalents. Because the accused devices literally infringe, a doctrine of equivalents inquiry is unnecessary. See ZMI Corp. v. Cardiac Resuscitator Corp., 844 F.2d at 1581, 6 USPQ2d at 1562 ("When literal infringement is not found, the equitable doctrine of equivalents comes into play.").

III. Invalidity

The district court held: "[i]f claim 1 were to be

given the broad meaning which plaintiff asserts, then the patent would be invalid for a failure to comply with the specification requirements of 35 U.S.C. § 112." 658 F.Supp. at 589, 3 USPQ2d at 1577-78. According to the district court a dose response study must be performed for materials other than stainless steel to determine the optimal electrical current to be supplied and this would involve "an undue amount of experimentation." *Id.*

In its cross-appeal Teletronics argues that the patent is invalid for non- enablement regardless of how the claims are interpreted because the disclosure does not bear a reasonable relationship to the scope of the claims.

Enablement is a legal determination which is reviewed as a matter of law. Raytheon Co. v. Roper Corp., 724 F.2d 951, 951-60, 220 USPQ 592, 599 (Fed. Cir. 1983). To be enabling under section 112, the patent must contain a description sufficient to enable one skilled in the art to make and use the claimed invention. *Id.* A patent may be enabling even though some experimentation is necessary; the amount of experimentation, however, must not be unduly extensive. Atlas Powder Co. v. E.I. du Pont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). A patent is presumed valid, and the burden of proving invalidity, whether under section 112 or otherwise, rests with the challenger. Invalidity must be proven by facts supported by clear and convincing evidence. Ralston Purina Co. v. Far-Mar- Co., Inc., 772 F.2d 1570, 1573-74, 227 USPQ 177, 178 (Fed. Cir. 1985) ("A party asserting invalidity based on 35 U.S.C. § 112 bears no less a burden . . . than any other patent challenger.") Thus, although not mentioned by the district court it is Teletronics' burden to show by facts supported by clear and convincing evidence that the patent was not enabling.

We note first that Teletronics admits that "[t]he patent does disclose how to successfully practice the invention -- if stainless *1223 steel electrodes and a current in the range of 5-20 microamperes is [sic] used." (Emphasis in original.) Lack of enablement is asserted on the basis that "the claims are not limited to the specific metal/current combination."

The district court thought that to determine the optimal electrical current for materials other than stainless steel a dose response study would be required and that this would involve an "undue amount of experimentation." The district court said "the patent does not tell a person reasonably skilled in

the art how to make and use this invention because it fails to teach how to select a level of current to promote bone formation and avoid fibrous tissue . . . formation from such current" for electrodes made of materials other than stainless steel. 658 F.Supp. at 589, 3 USPQ2d at 1578. It noted that "the patent does not contain an adequate description of the methodology for a dose response study for any cathode material other than stainless steel" and that "only those who were expert in the field and actually working with bone, doing electrical stimulation experiments . . . would know how to conduct" such a study. Moreover, the district court thought that the time and expense of such a study also indicated undue experimentation would be required.

[4] We are convinced that these findings and conclusions are insufficient to constitute clear and convincing proof of invalidity. First, it is undisputed that the patent disclosures are enabling with respect to stainless steel electrodes, with the range of current for such electrode set out in the specification. The specification shows this range of current was obtained by a dose response test. Next, according to the district court "those who were expert in the field and actually working with bone, doing electrical stimulation experiments . . . would know how to conduct a dose response study to determine the appropriate current to be used with other materials as electrodes." Id. The appropriate levels of current for other electrodes to promote bone growth and avoid fibrous tissue could, therefore, be determined. Finally, the emphasis by the district court on the time and cost of such studies is misplaced. While these factors may be taken into account, in the circumstances of this case we are unpersuaded that standing alone they show the experimentation to be excessive. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 107 S.Ct. 1606 (1987).

Since one embodiment is admittedly disclosed in the specification, along with the general manner in which its current range was ascertained, we are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation. See SRI Int'l v. Matsushita Elec. Corp. of America, 775 F.2d 1107, 1121, 227 USPQ 577, 586 (Fed.Cir. 1985) (the law does not require an applicant to describe in his specification every

conceivable embodiment of the invention); Hybritech Inc., 802 F.2d at 1384, 231 USPQ at 94 (the enablement requirement may be satisfied even though some experimentation is required). While perhaps fortuitous, as the district court found, the OSTEOSTIM device of Electronics used a current level of 20 microamperes, within the "substantially 5 microamperes to substantially 20 microamperes" range set forth in claim 5 and disclosed in the specification.

The district court also held that if claim 1 is read to mean that the current must be applied so as to minimize fibrous tissue formation then it would be invalid under 35 U.S.C. § 112 (1982) because it would be "impossible to determine when sufficient minimization takes place to determine what current range is involved." 658 F.Supp. at 589, 3 USPQ2d at 1578. The district court erred as a matter of law in this holding. Shatterproof Glass Corp. v. Libby-Owens Ford Co., 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985). Section 112, P2, requires only reasonable precision in delineating the bounds of the claimed invention. Id. Adjusting current so as to minimize fibrous tissue formation in other parts of the living being reasonably apprises those skilled in the art of the bounds of the claimed invention and is as precise as the subject matter permits. See id. Thus, we hold as a matter of law that the '841 patent is enabling and that the claims satisfy 35 U.S.C. § 112, P2.

In its cross appeal, Electronics argues that the specification is enabling only for the use of stainless steel while the claims are not limited in the types of material from which the electrodes can be made. It contends that the scope of the protection must bear a reasonable relationship to the scope of enablement, citing In re Fisher, 427 F.2d 833, 838-39, 166 USPQ 18, 23-24 (CCPA 1970) ("In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved."), *1224 and In re Bowen, 492 F.2d 859, 861-64, 181 USPQ 48, 50-52 (CCPA 1974) (section 112 requires that the scope of claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art). Fisher and Bowen both involved chemical reactions, recognized by our predecessor court as having a high degree of unpredictability and therefore requiring an increased enablement disclosure. Yet, in Bowen the board's non-enablement rejection was reversed where the "claims literally comprehend

numerous polymers in addition to the one specifically described in appellant's specification" because no persuasive reason was given by the Patent Office why the specification does not realistically enable one skilled in the art to practice the invention as broadly as it is claimed. In re Bowen, 492 F.2d at 863, 181 USPQ at 51-52. The same can be said here. The only impediments are the time and cost of a dose response study, which the district court found could be performed by "those who were expert in the field and actually working with bone, doing electrical stimulation experiments . . . , " i.e., those skilled in the art. Moreover, as we have noted, Teletronics's device using different electrode materials actually operated within the current parameters disclosed in the specification.

We conclude that the district court erred in its nonenablement conclusion and that facts supported by clear and convincing evidence of invalidity were not adduced.

In view of our decision, we need not consider the district court's denial of attorney fees to Teletronics.

Costs

The parties shall bear their respective costs.

AFFIRMED-IN-PART AND REVERSED-IN-PART

FN1 Teletronics has not appealed the district court's holdings on other issues it raised below.

FN2 There was some uncertainty as to which set of claims certain of these remarks applied, but the district court found that Amendments E and F related to the claims presented in Amendment D. Because we conclude that the district court erroneously limited the claims even if the remarks in controversy did apply to the claims which issued, we need not determine whether the district court correctly resolved this dispute.

FN3 The district court recognized that "[t]here are three possible positions for placement of the anode: on the skin, in soft tissue, and in the bone. Placement within the bone must be done carefully to avoid the

effect of insulation from the cortical bone."
658 F.Supp. at 583, 3 USPQ2d at 1573.

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In re Wands

Court of Appeals, Federal Circuit

No. 87-1454

Decided September 30, 1988

United States Patents Quarterly Headnotes

PATENTS

[1] Patentability/Validity -- Adequacy of disclosure (§ 115.12)

Data disclosed in application for immunoassay method patent, which shows that applicants screened nine of 143 cell lines developed for production of antibody necessary to practice invention, stored remainder of said cell lines, and found that four out of nine cell lines screened produced antibody falling within limitation of claims, were erroneously interpreted by Board of Patent Appeals and Interferences as failing to meet disclosure requirements of 35 USC 112, since board's characterization of stored cell lines as "failures" demonstrating unreliability of applicants' methods was improper in view of fact that such unscreened cell lines prove nothing concerning probability of success of person skilled in art attempting to obtain requisite antibodies using applicants' methods.

PATENTS

[2] Patentability/Validity -- Adequacy of disclosure (§ 115.12)

Disclosure in application for immunoassay method patent does not fail to meet enablement requirement of 35 USC 112 by requiring "undue experimentation," even though production of monoclonal antibodies necessary to practice invention first requires production and screening of numerous antibody producing cells or "hybridomas," since practitioners of art are prepared to screen negative hybridomas in order to find those that produce desired antibodies, since in monoclonal antibody art one "experiment" is not simply screening of one hybridoma but rather is entire attempt to make desired antibody, and since record indicates that amount of effort needed to obtain desired antibodies is not excessive, in view of applicants' success in

each attempt to produce antibody that satisfied all claim limitations.

***1400** Appeal from decision of Patent and Trademark Office, Board of Patent Appeals and Interferences.

Application for patent of Jack R. Wands, Vincent R. Zurawski, Jr., and Hubert J. P. Schoemaker, serial number 188,735. From decision of Board of Patent Appeals and Interferences affirming rejection of application, applicants appeal. Reversed; Newman, J., concurring in part and dissenting in part in separate opinion.

Jorge A. Goldstein, of Saidman, Sterne, Kessler & Goldstein (Henry N. Wixon, with them on brief), Washington, D.C., for appellant.

John H. Raubitschek, associate solicitor (Joseph F. Nakamura and Fred E. McKelvey, with him on brief), PTO, for appellee.

Before Smith, Newman, and Bissell, circuit judges.

Smith, J.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (board) affirming the rejection of all remaining claims in appellant's application for a patent, serial No. 188,735, entitled "Immunoassay Utilizing Monoclonal High Affinity IgM *1401 Antibodies," which was filed September 19, 1980. [FN1] The rejection under 35 U.S.C. § 112, first paragraph, is based on the grounds that appellant's written specification would not enable a person skilled in the art to make the monoclonal antibodies that are needed to practice the claimed invention without undue experimentation. We reverse.

I. Issue

The only issue on appeal is whether the board erred, as a matter of law, by sustaining the examiner's rejection for lack of enablement under 35 U.S.C. § 112, first paragraph, of all remaining claims in

appellants' patent application, serial No. 188,735.

II. Background

A. The Art.

The claimed invention involves immunoassay methods for the detection of hepatitis B surface antigen by using high-affinity monoclonal antibodies of the IgM isotype. Antibodies are a class of proteins (immunoglobulins) that help defend the body against invaders such as viruses and bacteria. An antibody has the potential to bind tightly to another molecule, which molecule is called an antigen. The body has the ability to make millions of different antibodies that bind to different antigens. However, it is only after exposure of an antigen that a complicated immune response leads to the production of antibodies against that antigen. For example, on the surface of hepatitis B virus particles there is a large protein called hepatitis B surface antigen (HBsAg). As its name implies, it is capable of serving as an antigen. During a hepatitis B infection (or when purified HBsAg is injected experimentally), the body begins to make antibodies that bind tightly and specifically to HBsAg. Such antibodies can be used as reagents for sensitive diagnostic tests (e.g., to detect hepatitis B virus in blood and other tissues, a purpose of the claimed invention). A method for detecting or measuring antigens by using antibodies as reagents is called an immunoassay.

Normally, many different antibodies are produced against each antigen. One reason for this diversity is that different antibodies are produced that bind to different regions (determinants) of a large antigen molecule such as HBsAg. In addition, different antibodies may be produced that bind to the same determinant. These usually differ in the tightness with which they bind to the determinant. Affinity is a quantitative measure of the strength of antibody-antigen binding. Usually an antibody with a higher affinity for an antigen will be more useful for immunological diagnostic tests than one with a lower affinity. Another source of heterogeneity is that there are several immunoglobulin classes or isotypes. Immunoglobulin G (IgG) is the most common isotype in serum. Another isotype, immunoglobulin M (IgM), is prominent early in the immune response. IgM molecules are larger than IgG molecules, and have 10 antigen-binding sites instead of the 2 that are present in IgG. Most immunoassay methods use IgG, but the claimed invention uses only IgM antibodies.

For commercial applications there are many disadvantages to using antibodies from serum. Serum contains a complex mixture of antibodies against the antigen of interest within a much larger pool of antibodies directed at other antigens. There are available only in a limited supply that ends when the donor dies. The goal of monoclonal antibody technology is to produce an unlimited supply of a single purified antibody.

The blood cells that make antibodies are lymphocytes. Each lymphocyte makes only one kind of antibody. During an immune response, lymphocytes exposed to their particular antigen divide and mature. Each produces a clone of identical daughter cells, all of which secrete the same antibody. Clones of lymphocytes, all derived from a single lymphocyte, could provide a source of a single homogeneous antibody. However, lymphocytes do not survive for long outside of the body in cell culture.

Hybridoma technology provides a way to obtain large numbers of cells that all produce the same antibody. This method takes advantage of the properties of myeloma cells derived from a tumor of the immune system. The cancerous myeloma cells can divide indefinitely in vitro. They also have the potential ability to secrete antibodies. By appropriate experimental manipulations, a myeloma cell can be made to fuse with a lymphocyte to produce a single hybrid cell (hence, a hybridoma) that contains the genetic material of both cells. The hybridoma secretes the same antibody that was made by its parent lymphocyte, but acquires the capability of the myeloma cell to divide and grow indefinitely in cell culture. Antibodies produced by a clone of hybridoma cells (i.e., by hybridoma *1402 cells that are all progeny of a single cell) are called monoclonal antibodies. [FN2]

B. The Claimed Invention.

The claimed invention involves methods for the immunoassay of HBsAg by using high-affinity monoclonal IgM antibodies. Jack R. Wands and Vincent R. Zurawski, Jr., two of the three coinventors of the present application, disclosed methods for producing monoclonal antibodies against HBsAg in United States patent No. 4,271,145 (the '145 patent), entitled "Process for Producing Antibodies to Hepatitis Virus and Cell Lines Therefor," which patent issued on June 2, 1981. The '145 patent is incorporated by reference into the application on

appeal. The specification of the '145 patent teaches a procedure for immunizing mice against HBsAg, and the use of lymphocytes from these mice to produce hybridomas that secrete monoclonal antibodies specific for HBsAg. The '145 patent discloses that this procedure yields both IgG and IgM antibodies with high-affinity binding to HBsAg. For the stated purpose of complying with the best mode requirement of 35 U.S.C. § 112, first paragraph, a hybridoma cell line that secretes IgM antibodies against HBsAg (the 1F8 cell line) was deposited at the American Type Culture Collection, a recognized cell depository, and became available to the public when the '145 patent issued.

The application on appeal claims methods for immunoassay of HBsAg using monoclonal antibodies such as those described in the '145 patent. Most immunoassay methods have used monoclonal antibodies of the IgG isotype. IgM antibodies were disfavored in the prior art because of their sensitivity to reducing agents and their tendency to self-aggregate and precipitate. Appellants found that their monoclonal IgM antibodies could be used for immunoassay of HbsAg with unexpectedly high sensitivity and specificity. Claims 1, 3, 7, 8, 14, and 15 are drawn to methods for the immunoassay of HBsAg using high-affinity IgM monoclonal antibodies. Claims 19 and 25-27 are for chemically modified (e.g., radioactively labeled) monoclonal IgM antibodies used in the assays. The broadest method claim reads:

1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:

contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and

determining the presence of said substance in said sample;

wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10 super9 M- super1.

Certain claims were rejected under 35 U.S.C. § 103; these rejections have not been appealed. Remaining claims 1, 3, 7, 8, 14, 15, 19, and 25-27 were rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the disclosure would not enable a person

skilled in the art to make and use the invention without undue experimentation. The rejection is directed solely to whether the specification enables one skilled in the art to make the monoclonal antibodies that are needed to practice the invention. The position of the PTO is that data presented by Wands show that the production of high-affinity IgM anti-HBsAg antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies.

III. Analysis

A. Enablement by Deposit of Micro-organisms and Cell Lines.

The first paragraph of 35 U.S.C. § 112 requires that the specification of a patent must enable a person skilled in the art to make and use the claimed invention. "Patents * * * are written to enable those skilled in the art to practice the invention." [FN3] A patent need not disclose what is well known in the art. [FN4] Although we review underlying facts found by the board under a "clearly erroneous" standard, [FN5] we review enablement as a question of law. [FN6]

Where an invention depends on the use of living materials such as microorganisms or *1403 cultured cells, it may be impossible to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure. One means that has been developed for complying with the enablement requirement is to deposit the living materials in cell depositories which will distribute samples to the public who wish to practice the invention after the patent issues. [FN7] Administrative guidelines and judicial decisions have clarified the conditions under which a deposit of organisms can satisfy the requirements of section 112. [FN8] A deposit has been held necessary for enablement where the starting materials (i.e., the living cells used to practice the invention, or cells from which the required cells can be produced) are not readily available to the public. [FN9] Even when starting materials are available, a deposit has been necessary where it would require undue experimentation to make the cells of the invention from the starting materials. [FN10]

In addition to satisfying the enablement requirement, deposit of organisms also can be used to establish the filing date of the application as the

prima facie date of invention, [FN11] and to satisfy the requirement under 35 U.S.C. § 114 that the PTO be guaranteed access to the invention during pendency of the application. [FN12] Although a deposit may serve these purposes, we recognized, in *In re Lundak*, [FN13] that these purposes, nevertheless, may be met in ways other than by making a deposit.

A deposit also may satisfy the best mode requirement of section 112, first paragraph, and it is for this reason that the 1F8 hybridoma was deposited in connection with the '145 patent and the current application. Wands does not challenge the statements by the examiner to the effect that, although the deposited 1F8 line enables the public to perform immunoassays with antibodies produced by that single hybridoma, the deposit does not enable the generic claims that are on appeal. The examiner rejected the claims on the grounds that the written disclosure was not enabling and that the deposit was inadequate. Since we hold that the written disclosure fully enables the claimed invention, we need not reach the question of the adequacy of deposits.

B. Undue Experimentation.

Although inventions involving microorganisms or other living cells often can be enabled by a deposit, [FN14] a deposit is not always necessary to satisfy the enablement requirement. [FN15] No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation. [FN16] Whether the specification in an application involving living cells (here, hybridomas) is enabled without a deposit must be decided on the facts of the particular case. [FN17]

Appellants contend that their written specification fully enables the practice of *1404 their claimed invention because the monoclonal antibodies needed to perform the immunoassays can be made from readily available starting materials using methods that are well known in the monoclonal antibody art. Wands states that application of these methods to make high-affinity IgM anti- HBsAg antibodies requires only routine screening, and that does not amount to undue experimentation. There is no challenge to their contention that the starting materials (i.e., mice, HBsAg antigen, and myeloma cells) are available to the public. The PTO concedes that the methods used to prepare hybridomas and to

screen them for high-affinity IgM antibodies against HBsAg were either well known in the monoclonal antibody art or adequately disclosed in the '145 patent and in the current application. This is consistent with this court's recognition with respect to another patent application that methods for obtaining and screening monoclonal antibodies were well known in 1980. [FN18] The sole issue is whether, in this particular case, it would require undue experimentation to produce high-affinity IgM monoclonal antibodies.

Enablement is not precluded by the necessity for some experimentation such as routine screening. [FN19] However, experimentation needed to practice the invention must not be undue experimentation. [FN20] "the key word is 'undue,' not 'experimentation.' " [FN21]

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir. 1971), cert. denied, 404 U.S. 1018 [172 USPQ 257] (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed * * *. [FN22]

The term "undue experimentation" does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. [FN23] Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. The board concluded that undue experimentation would be needed to practice the invention on the basis of experimental data presented by Wands. These data are not in dispute. However, Wands and the board disagree strongly on the conclusion that should be drawn from that data.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. [FN24] They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. [FN25]

In order to understand whether the rejection was proper, it is necessary to discuss further the methods for making specific monoclonal antibodies. The first step for making monoclonal antibodies is to immunize an animal. The '145 patent provides a detailed description of procedures for immunizing a specific strain of mice against HBsAg. Next the spleen, an organ rich in lymphocytes, is removed and the lymphocytes are separated from the other spleen cells. The lymphocytes are mixed with myeloma cells, and the mixture is treated to cause a few of the cells to fuse with each other. Hybridoma cells that secrete the desired antibodies then must be isolated from the enormous number of other cells in the mixture. This is done through a series of screening procedures.

The first step is to separate the hybridoma cells from unfused lymphocytes and myeloma cells. The cells are cultured in a medium *1405 in which all the lymphocytes and myeloma cells die, and only the hybridoma cells survive. The next step is to isolate and clone hybridomas that make antibodies that bind to the antigen of interest. Single hybridoma cells are placed in separate chambers and are allowed to grow and divide. After there are enough cells in the clone to produce sufficient quantities of antibody to analyze, the antibody is assayed to determine whether it binds to the antigen. Generally, antibodies from many clones do not bind the antigen, and these clones are discarded. However, by screening enough clones (often hundreds at a time), hybridomas may be found that secrete antibodies against the antigen of interest.

Wands used a commercially available radioimmunoassay kit to screen clones for cells that produce antibodies directed against HBsAg. In this assay the amount of radioactivity bound gives some indication of the strength of the antibody- antigen binding, but does not yield a numerical affinity constant, which must be measured using the more laborious Scatchard analysis. In order to determine which anti-HBsAg antibodies satisfy all of the limitations of appellants' claims, the antibodies require further screening to select those which have an IgM isotype and have a binding affinity constant of at least 10 super9 M- super1 . [FN26] The PTO does not question that the screening techniques used by Wands were well known in the monoclonal antibody art.

During prosecution Wands submitted a declaration under 37 C.F.R. § 1.132 providing information about all of the hybridomas that appellants had produced before filing the patent application. The first four fusions were unsuccessful and produced no hybridomas. The next six fusion experiments all produced hybridomas that made antibodies specific for HBsAg. Antibodies that bound at least 10,000 cpm in the commercial radioimmunoassay were classified as "high binders." Using this criterion, 143 high-binding hybridomas were obtained. In the declaration, Wands stated that [FN27]

It is generally accepted in the art that, among those antibodies which are binders with 50,000 cpm or higher, there is a very high likelihood that high affinity (K_a [greater than] 10 super9 M- super1) antibodies will be found. However, high affinity antibodies can also be found among high binders of between 10,000 and 50,000, as is clearly demonstrated in the Table.

The PTO has not challenged this statement.

The declaration stated that a few of the high-binding monoclonal antibodies from two fusions were chosen for further screening. The remainder of the antibodies and the hybridomas that produced them were saved by freezing. Only nine antibodies were subjected to further analysis. Four (three from one fusion and one from another fusion) fell within the claims, that is, were IgM antibodies and had a binding affinity constant of at least 10 super9 M- super1 . Of the remaining five antibodies, three were found to be IgG, while the other two were IgM for which the affinity constants were not measured (although both showed binding well above 50,000 cpm).

Apparently none of the frozen cell lines received any further analysis. The declaration explains that after useful high-affinity IgM monoclonal antibodies to HBsAg had been found, it was considered unnecessary to return to the stored antibodies to screen for more IgMs. Wands says that the existence of the stored hybridomas was disclosed to the PTO to comply with the requirement under 37 C.F.R. § 1.56 that applicants fully disclose all of their relevant data, and not just favorable results. [FN28] How these stored hybridomas are viewed is central to the positions of the parties.

The position of the board emphasizes the fact that since the stored cell lines were not completely tested, there is no proof that any of them are IgM antibodies

with a binding affinity constant of at least 10 super9 M- super1 . Thus, only 4 out of 143 hybridomas, or 2.8 percent, were proved to fall within the claims. Furthermore, antibodies that were proved to be high-affinity IgM came from only 2 of 10 fusion experiments. These statistics are viewed by the board as evidence that appellants' methods were not predictable or reproducible. The board concludes that Wands' low rate of demonstrated success shows that a person skilled in the art would have to *1406 engage in undue experimentation in order to make antibodies that fall within the claims.

Wands views the data quite differently. Only nine hybridomas were actually analyzed beyond the initial screening for HBsAg binding. Of these, four produced antibodies that fell within the claims, a respectable 44 percent rate of success. (Furthermore, since the two additional IgM antibodies for which the affinity constants were never measured showed binding in excess of 50,000 cpm, it is likely that these also fall within the claims.) Wands argues that the remaining 134 unanalyzed, stored cell lines should not be written off as failures. Instead, if anything, they represent partial success. Each of the stored hybridomas had been shown to produce a high-binding antibody specific for HBsAg. Many of these antibodies showed binding above 50,000 cpm and are thus highly likely to have a binding affinity constant of at least 10 super9 M- super1 . Extrapolating from the nine hybridomas that were screened for isotype (and from what is well known in the monoclonal antibody art about isotype frequency), it is reasonable to assume that the stored cells include some that produce IgM. Thus, if the 134 incompletely analyzed cell lines are considered at all, they provide some support (albeit without rigorous proof) to the view that hybridomas falling within the claims are not so rare that undue experimentation would be needed to make them.

The first four fusion attempts were failures, while high-binding antibodies were produced in the next six fusions. Appellants contend that the initial failures occurred because they had not yet learned to fuse cells successfully. Once they became skilled in the art, they invariably obtained numerous hybridomas that made high-binding antibodies against HBsAg and, in each fusion where they determined isotype and binding affinity they obtained hybridomas that fell within the claims.

Wands also submitted a second declaration under 37 C.F.R. § 1.132 stating that after the patent application was submitted they performed an eleventh fusion

experiment and obtained another hybridoma that made a high-affinity IgM anti-HBsAg antibody. No information was provided about the number of clones screened in that experiment. The board determined that, because there was no indication as to the number of hybridomas screened, this declaration had very little value. While we agree that it would have been preferable if Wands had included this information, the declaration does show that when appellants repeated their procedures they again obtained a hybridoma that produced an antibody that fit all of the limitations of their claims.

[1] We conclude that the board's interpretation of the data is erroneous. It is strained and unduly harsh to classify the stored cell lines (each of which was proved to make high-binding antibodies against HBsAg) as failures demonstrating that Wands' methods are unpredictable or unreliable. [FN29] At worst, they prove nothing at all about the probability of success, and merely show that appellants were prudent in not discarding cells that might someday prove useful. At best, they show that high-binding antibodies, the starting materials for IgM screening and Scatchard analysis, can be produced in large numbers. The PTO's position leads to the absurd conclusion that the more hybridomas an applicant makes and saves without testing the less predictable the applicant's results become. Furthermore, Wands' explanation that the first four attempts at cell fusion failed only because they had not yet learned to perform fusions properly is reasonable in view of the fact that the next six fusions were all successful. The record indicates that cell fusion is a technique that is well known to those of ordinary skill in the monoclonal antibody art, and there has been no claim that the fusion step should be more difficult or unreliable where the antigen is HBsAg than it would be for other antigens.

[2] When Wands' data is interpreted in a reasonable manner, analysis considering the factors enumerated in *Ex parte Forman* leads to the conclusion that undue experimentation would not be required to practice the invention. Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

The nature of monoclonal antibody technology is that it involves screening hybridomas to determine

which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. However, it seems unlikely that undue *1407 experimentation would be defined in terms of the number of hybridomas that were never screened. Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics. Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations. Reasonably interpreted, Wands' record indicates that, in the production of high-affinity IgM antibodies against HBsAG, the amount of effort needed to obtain such antibodies is not excessive. Wands' evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure. [FN30]

IV. Conclusion

Considering all of the factors, we conclude that it would not require undue experimentation to obtain antibodies needed to practice the claimed invention. Accordingly, the rejection of Wands' claims for lack of enablement under 35 U.S.C. § 112, first paragraph, is reversed.

REVERSED

FN1 In re Wands, Appeal No. 673-76 (Bd. Pat. App. & Int. Dec. 30, 1986).

FN2 For a concise description of monoclonal antibodies and their use in immunoassay see Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1368-71, 231 USPQ 81, 82-83 (Fed. Cir. 1986), cert. denied, 107 S.Ct. 1606 (1987).

FN3 W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

FN4 Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

FN5 Coleman v. Dines, 754 F.2d 353, 356, 224 USPQ 857, 859 (Fed. Cir. 1985).

FN6 Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 1268, 229 USPQ 805, 810 (Fed. Cir. 1986), cert. denied, 107 S.Ct. 875 (1987); Raytheon Co. v. Roper Corp., 724 F.2d 951, 960 n.6, 220 USPQ 592, 599 n.6 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 [225 USPQ 232] (1984).

FN7 In re Argoudelis, 434 F.2d 1390, 1392-93, 168 USPQ 99, 101-02 (CCPA 1970).

FN8 In re Lundak, 773 F.2d 1216, 227 USPQ 90 (Fed. Cir. 1985); Feldman v. Aunstrup, 517 F.2d 1351, 186 USPQ 108 (CCPA 1975), cert. denied, 424 U.S. 912 [188 USPQ 720] (1976); Manual of Patent Examining Procedure (MPEP) 608.01 (p)(C) (5th ed. 1983, rev. 1987). See generally Hampar, Patenting of Recombinant DNA Technology: The Deposit Requirement, 67 J. Pat. Trademark Off. Soc'y 569 (1985).

FN9 In re Jackson, 217 USPQ 804, 807-08 (Bd. App. 1982) (strains of a newly discovered species of bacteria isolated from nature); Feldman, 517 F.2d 1351, 186 USPQ 108 (uncommon fungus isolated from nature); In re Argoudelis, 434 F.2d at 1392, 168 USPQ at 102 (novel strain of antibiotic-producing microorganism isolated from nature); In re Kropp, 143 USPQ 148, 152 (Bd. App. 1959) (newly discovered microorganism isolated from soil).

FN10 Ex parte Forman, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (genetically engineered bacteria where the specification provided insufficient information about the amount of time and effort required); In re Lundak, 773 F.2d 1216, 227 USPQ 90 (unique cell line produced from another cell line by mutagenesis).

FN11 In re Lundak, 773 F.2d at 1222, 227 USPQ at 95-96; In re Feldman, 517 F.2d at 1355, 186 USPQ at 113; In re Argoudelis, 434 F.2d at 1394-96, 168 USPQ at 103-04 (Baldwin, J. concurring).

FN12 In re Lundak, 773 F.2d at 1222, 227 USPQ at 95-96; In re Feldman, 517 F.2d at 1354, 186 USPQ at 112.

FN13 In re Lundak, 773 F.2d at 1222, 227 USPQ at 95-96.

FN14 In re Argoudelis, 434 F.2d at 1393, 168 USPQ at 102.

FN15 Tabuchi v. Nubel, 559 F.2d 1183, 194 USPQ 521 (CCPA 1977).

FN16 Id. at 1186-87, 194 USPQ at 525; Merck & Co. v. Chase Chem. Co., 273 F.Supp. 68, 77, 155 USPQ 139, 146 (D.N.J. 1967); Guaranty Trust Co. v. Union Solvents Corp., 54 F.2d 400, 403-06, 12 USPQ 47, 50-53 (D. Del. 1931), aff'd, 61 F.2d 1041, 15 USPQ 237 (3d Cir. 1932), cert. denied, 288 U.S. 614 (1933); MPEP 608.01 (p)(C) ("No problem exists when the microorganisms used are known and readily available to the public.").

FN17 In re Jackson, 217 USPQ at 807; see In re Metcalfe, 410 F.2d 1378, 1382, 161 USPQ 789, 792 (CCPA 1969).

FN18 Hybritech, 802 F.2d at 1384, 231 USPQ at 94.

FN19 Id.; Atlas Powder Co. v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984); In re Angstadt, 537 F.2d at 502-504, 190 USPQ at 218; In re Geerdes, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); Mineral Separation, Ltd. v. Hyde, 242 U.S. 261, 270-71 (1916).

FN20 Hybritech, 802 F.2d at 1384, 231 USPQ at 94; W.L. Gore, 721 F.2d at 1557, 220 USPQ at 316; In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977) (Miller, J., concurring).

FN21 In re Angstadt, 537 F.2d at 504, 190 USPQ at 219.

FN22 In re Jackson, 217 USPQ at 807.

FN23 See Hybritech, 802 F.2d at 1384, 231 USPQ at 94; Atlas Powder, 750 F.2d at 1576, 224 USPQ at 413.

FN24 Ex parte Forman, 230 USPQ at 547.

FN25 Id.; see In re Colianni, 561 F.2d at 224, 195 USPQ at 153 (Miller, J., concurring); In re Rainer, 347 F.2d 574, 577, 146 USPQ 218, 221 (CCPA 1965).

FN26 The examiner, the board, and Wands all point out that, technically, the strength of antibody-HBsAg binding is measured as avidity, which takes into account multiple determinants on the HBsAg molecule, rather than affinity. Nevertheless, despite this correction, all parties then continued to use the term "affinity." We will use the terminology of the parties. Following the usage of the parties, we will also use the term "high- affinity" as essentially synonymous with "having a binding affinity constant of at least 10 super9 M- super1."

FN27 A table in the declaration presented

the binding data for antibodies from every cell line. Values ranged from 13,867 to 125,204 cpm, and a substantial proportion of the antibodies showed binding greater than 50,000 cpm. In confirmation of Dr. Wand's statement, two antibodies with binding less than 25,000 cpm were found to have affinity constants greater than 10 super9 M- super1 .

FN28 See Rohm & Haas Co. v. Crystal Chem. Co., 722 F.2d 1556, 220 USQ 98 (Fed. Cir. 1983).

FN29 Even if we were to accept the PTO's 2.8% success rate, we would not be required to reach a conclusion of undue experimentation. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff.

FN30 In re Strahilevitz, 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982).

Newman, J., concurring in part, dissenting in part.

A

I concur in the court's holding that additional samples of hybridoma cell lines that produce these high-affinity IgM monoclonal antibodies need not be deposited. This invention, as described by Wands, is not a selection of a few rare cells from many possible cells. To the contrary, Wands states that all monoclonally produced IgM antibodies to hepatitis B surface antigen have the desired high avidity and other favorable properties, and that all are readily preparable by now-standard techniques.

Wands states that his United States Patent No. 4,271,145 describes fully operable techniques, and is distinguished from his first four failed experiments that are referred to in the Rule 132 affidavit. Wands argues that these biotechnological mechanisms are relatively well understood and that the preparations can be routinely duplicated by those of skill in this art, as in Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 107 S.Ct. 1606 (1987). I agree that it is not necessary that there be a deposit of

multiple exemplars of a cell system that is readily reproduced by known, specifically identified techniques.

B

I would affirm the board's holding that Wands has not complied with 35 U.S.C. § 112, first paragraph, in that he has not provided data sufficient to support the breadth of his generic claims. Wands' claims on appeal include the following:

19. Monoclonal high affinity IgM antibodies immunoreactive with HBsAg determinants, wherein said antibodies are coupled to an insoluble solid phase, and wherein the binding affinity constant of said antibodies for said HBsAg determinants is at least 10 super9 M- super1 .
26. Monoclonal high affinity IgM antibodies immunoreactive with hepatitis B surface antigen.

Wands states that he obtained 143 "high binding monoclonal antibodies of the right specificity" in the successful fusions; although he does not state how they were determined to be high binding or of the right specificity, for Wands also states that only nine of these 143 were tested.

Of these nine, four (three from one fusion and one from another fusion) were found to have the claimed high affinity and to be of the IgM isotype. Wands states that the other five were either of a different isotype or their affinities were not determined. (This latter statement also appears to contradict his statement that all 143 were "high binding".)

Wands argues that a "success rate of four out of nine", or 44.4%, is sufficient to support claims to the entire class. The Commissioner deems the success rate to be four out of 143, or 2.8%; to which Wands responds with statistical analysis as to how unlikely it is that Wands selected the only four out of 143 that worked. Wands did not, however, prove the right point. The question is whether Wands, by testing nine out of 143 (the Commissioner points out that the randomness of the sample was not established), and finding that four out of the nine had the desired properties, has provided sufficient experimental support for the breadth of the requested claims, in the context that "experiments *1408 in genetic engineering produce, at best, unpredictable results", quoting from Ex parte Forman, 230 USPQ 546, 547 (Bd.Pat.App. and Int. 1986).

The premise of the patent system is that an inventor, having taught the world something it didn't know, is encouraged to make the product available for public and commercial benefit, by governmental grant of the right to exclude others from practice of that which the inventor has disclosed. The boundary defining the excludable subject matter must be carefully set: it must protect the inventor, so that commercial development is encouraged; but the claims must be commensurate with the inventor's contribution. Thus the specification and claims must meet the requirements of 35 U.S.C. § 112. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 23-24 (CCPA 1970).

As the science of biotechnology matures the need for special accommodation, such as the deposit of cell lines or microorganisms, may diminish; but there remains the body of law and practice on the need for sufficient disclosure, including experimental data when appropriate, that reasonably support the scope of the requested claims. That law relates to the sufficiency of the description of the claimed invention, and if not satisfied by deposit, must independently meet the requirements of Section 112.

Wands is not claiming a particular, specified IgM antibody. He is claiming all such monoclonal antibodies in assay for hepatitis B surface antigen, based on his teaching that such antibodies have uniformly reproducible high avidity, free of the known disadvantages of IgM antibodies such as tendency to precipitate or aggregate. It is incumbent upon Wands to provide reasonable support for the proposed breadth of his claims. I agree with the Commissioner that four exemplars shown to have the desired properties, out of the 143, do not provide adequate support.

Wands argues that the law should not be "harsher" where routine experiments take a long time. However, what Wands is requesting is that the law be less harsh. As illustrated in extensive precedent on the question of how much experimentation is "undue", each case must be determined on its own facts. See, e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984); In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976); In re Cook, 439 F.2d 730, 734-35, 169 USPQ 298, 302-03 (CCPA 1971).

The various criteria to be considered in determining whether undue experimentation is required are discussed in, for example, Fields v. Conover, 443

F.2d 1386, 170 USPQ 276 (CCPA 1971); In re Rainer, 347 F.2d 574, 146 USPQ 218 (CCPA 1965); Ex parte Forman, 230 USPQ at 547. Wands must provide sufficient data or authority to show that his results are reasonably predictable within the scope of the claimed generic invention, based on experiment and/or scientific theory. In my view he has not met this burden.

C.A.Fed.

8 U.S.P.Q.2d 1400

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H
The Johns Hopkins University
v.
Cellpro Inc.

U.S. Court of Appeals Federal Circuit

Nos. 97-1495, 98-1017

Decided August 11, 1998

United States Patents Quarterly Headnotes

PATENTS

[1] Patent construction -- Claims -- Broad or narrow (Section 125.1303)

Patent construction -- Claims -- Defining terms (Section 125.1305)

Federal district court did not err in construing claim of patent for suspension of immature blood cells, which includes limitation that cell suspension be "substantially free" of mature cells, to require no more than 10 percent mature cells, since claim should be construed to encompass at least one disclosed embodiment in written description, since table in specification, which describes only embodiment of invention disclosed therein, discloses cell suspension containing 10 percent mature lymphoid cells, and since applicant's statement that claimed invention does not contain T-cells does not mean that cell suspension cannot contain measurable amounts of other mature myeloid and lymphoid cells.

PATENTS

[2] Patent construction -- Claims -- In general (Section 125.1301)

Federal district court erred in determining that patent infringement defendant, which had chosen not to rely on particular prior art reference in first trial on issue of obviousness, waived its right to rely on that reference in second trial following grant of plaintiffs' new trial motion, since new prior art became potentially relevant when court adopted broadened construction of claim at issue after first trial, since fact that defendant knew of reference before first trial but chose not to rely upon it at that time cannot constitute waiver of opportunity to apply that art against claim whose construction was not yet finally determined, and since pretrial order from first trial

did not control range of evidence to be considered in second trial.

PATENTS

[3] Infringement -- Construction of claims (Section 120.03)

Patent construction -- Claims -- Defining terms (Section 125.1305)

Federal district court properly determined that clause in claim of patent for monoclonal antibodies useful in producing purified suspension of blood "stem" cells refers to antigen known by those of ordinary skill in field as "the CD34 antigen," since record makes clear that term "the CD34 antigen" is synonymous with "My-10" antigen discovered by inventor, which appears on surface of immature stem cells and is recognized by monoclonal antibodies of invention, and since there is no evidence to support theory that phrase "the CD34 antigen" encompasses genus of antigens, although CD34 antigen contains number of epitopes on its surface to which various CD34 antibodies can bind; defendant's "12.8" antibody, which binds to CD34 antigen, literally infringes claim, even though it binds to different epitope than does antibody disclosed in patent.

PATENTS

[4] Patentability/Validity -- Specification -- Enablement (Section 115.1105)

Infringement defendant's evidence of undue experimentation is insufficient to preclude entry of summary judgment for plaintiffs on issue of enablement, since defendant failed to offer evidence that individuals who were allegedly unsuccessful in producing claimed antibody using technique disclosed in specification were of ordinary skill in art, since expert who testified that he was unsuccessful in making antibody did not use screening technique disclosed in specification, since expert who concluded that it was more difficult to produce claimed antibody than other monoclonal antibodies did not attribute this difficulty to any shortcomings in disclosure of patent, and since allegation that claimed antibody cannot be made by using alternative to preferred mode is irrelevant, in that enablement requirement is met if description enables any mode of making and using invention.

PATENTS

[5] Infringement -- Willful (Section 120.16)

JUDICIAL PRACTICE AND PROCEDURE

Procedure – Evidence – In general (Section 410.3701)

Existence of favorable liability verdict for patent infringement defendant in first trial was properly excluded from evidence in subsequent trial of willfulness and damages issues, conducted after grant of new trial and liability judgment in favor of plaintiffs, since prior jury verdict had no bearing upon willfulness of defendant's infringement on dates it received notice of plaintiffs' patent rights, and since consideration of earlier verdict, which was ultimately determined to be premised upon erroneous claim construction, had significant potential to confuse jury.

by ordering repatriation and destruction of vials containing cell line used to produce infringing antibodies, since exported vials were created by defendant prior to issuance of patent and used in Canada to supply markets outside U.S., since mere possession of product which becomes covered by subsequently issued patent does not constitute infringement, since neither export nor use in foreign country of product covered by U.S. patent constitutes infringement, since fact that defendant used other vials from cell bank in infringing manner does not "taint" exported vials with infringement, and since order, therefore, does not enjoin activities that either have infringed patent or are likely to do so, and does not prevent infringement.

PATENTS

[6] Infringement – Willful (Section 120.16)

JUDICIAL PRACTICE AND PROCEDURE

Procedure – Jury trials (Section 410.42)

Jury instruction on issue of willful infringement of patents, stating that no reasonable jury could fail to find that defendant infringed valid patents, did not improperly force jury to find willful infringement, since such statement says nothing about defendant's willfulness, which is reflective of infringer's culpability, and since statements concerning infringement and validity were properly designed to ensure that willfulness jury did not collaterally consider defendant's liability for infringement, which had already been determined by court.

PATENTS

[7] Infringement – Willful (Section 120.16)

Jury's finding that defendant willfully infringed patents in suit is supported by substantial evidence, since attorney opinion letters defendant obtained did not attempt to link disclosures of prior art references relied upon to establish anticipation and obviousness with limitations of claims of patents in suit, and did not express opinion concerning infringement of broadest claims, and since it is reasonable to conclude that representative of defendant who received opinion letters should have been on notice concerning their obvious shortcomings, and, accordingly, of impropriety of defendant's course of action.

REMEDIES

Particular patents – Chemical – Stem cells and antibodies

4,714,680, Civin, human stem cells, summary judgment holding patent not invalid vacated.

4,965,204, Civin, human stem cells and monoclonal antibodies, summary judgment holding patent infringed and not invalid affirmed.

***1706** Appeal from the U.S. District Court for the District of Delaware, McKelvie, J.

Action by The Johns Hopkins University, Baxter Healthcare Corp., and Becton Dickinson & Co. against Cellpro Inc. for patent infringement, in which defendant counterclaimed for declaratory judgment of patent invalidity and non-infringement. Defendant appeals from judgments finding infringement of both patents in suit, from summary judgment for plaintiffs on enablement and written description defenses, from judgment sustaining jury's verdict of willful infringement, from award of treble damages, and from order requiring certain vials of defendant's product to be repatriated to United States and destroyed. Affirmed in part, vacated in part, and remanded.

Related decision: 34 USPQ2d 1276.

Donald R. Ware, Peter B. Ellis, and Philip C. Swain, of Foley, Hoag & Eliot, Boston, Mass.; Michael C. Schiffer, Baxter Healthcare Corp., Irvine, Calif., for plaintiffs-appellees.

REMEDIES

[8] Non-monetary and injunctive – Equitable relief – Seizure; forfeiture (Section 505.0703)

Federal district court exceeded scope of its authority

Don W. Martens, Joseph R. Re, Michael K. Friedland, and Dale C. Hunt, of Knobbe, Martens, Olson & Bear, Newport Beach, Calif.; Gary D. Wilson and Steven M. Dunne, of Wilmer, Cutler & Pickering, Washington, D.C.; Robert C. Weiss, Allan W. Jansen, and Jerrold B. Reilly, of Lyon & Lyon, Los Angeles, Calif., for defendant-appellant.

Before Lourie, circuit judge, Smith, senior circuit judge, and Schall, circuit judge.

Lourie, J.

CellPro, Inc. appeals from the decision of the United States District Court for the District of Delaware in favor of Johns Hopkins University, Baxter Healthcare Corporation, and Becton Dickinson and Company (collectively, Hopkins) in their patent infringement suit against CellPro. The court (1) granted Hopkins' motion for judgment as a matter of law that CellPro infringed claims *1707 1-5 of U.S. Patent B1 4,714,680, see Johns Hopkins Univ. v. CellPro, 931 F. Supp. 303, 319 (D. Del. 1996) [hereinafter Hopkins I]; (2) excluded certain evidence allegedly relevant to the obviousness of those claims, see Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Oct. 1, 1996); id. (D. Del. Jan. 29, 1997); (3) granted Hopkins' motion for summary judgment that CellPro infringed claims 1 and 4 of U.S. Patent 4,965,204, see id. (D. Del. Nov. 27, 1996); (4) granted Hopkins' summary judgment motion concerning CellPro's enablement and written description defenses, see id. (D. Del. Feb. 24, 1997) (enablement); id. (D. Del. Oct. 31, 1996) (written description); (5) sustained the jury's verdict of willful infringement and treble damages, see John [s] Hopkins Univ. v. CellPro, 978 F. Supp. 184 (D. Del. 1997) [hereinafter Hopkins II]; and (6) ordered certain vials of CellPro's product to be repatriated to the United States and destroyed, see Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Jul. 24, 1997). We affirm-in-part, vacate-in-part, and remand.

BACKGROUND

A. The Technology

The '680 and '204 patents (the "Civin patents") issued from continuations of the same parent application [FN1] and pertain generally to relatively

pure suspensions of immature blood cells and monoclonal antibodies used to produce such suspensions. These immature cells, known as "stem" cells, develop into many different forms of mature blood cells, including lymphoid cells (T-cells and B-cells) and myeloid cells (red cells, platelets and granulocytes). See generally Hopkins I, 931 F. Supp. at 308 (discussing the physiology of blood).

Because stem cells are killed by radiation therapy, these cells must be replaced in leukemia patients who have undergone this treatment. While bone marrow transplants can provide a patient with new stem cells, this procedure carries risks. Notably, the presence of mature cells in transplanted bone marrow can give rise to Graft Versus Host Disease (GVHD), a potentially fatal condition. [FN2] Accordingly, one of the stated objectives of the invention of the Civin patents "is to provide a method for preparing a cell population useful for stem cell transplantation that is enriched in immature marrow cells and substantially free of mature myeloid and lymphoid cells." '680 patent, col. 2, ll. 1-5; see also Hopkins I, 931 F. Supp. at 309.

In the early 1980s, scientists began making monoclonal antibodies [FN3] that would recognize and bind to the antigens contained on the surface of blood cells. Once an antibody binds to an antigen on a cell surface, that cell is flagged and can be separated from other cells using known techniques such as the "FACS" method. [FN4] Monoclonal antibodies, which are uniform in their binding properties, are produced by cloned cells known as hybridomas. [FN5] Hybridomas grow and reproduce rapidly and can be frozen for later use to produce additional monoclonal antibodies.

Dr. Curt Civin, the inventor named in the '680 and '204 patents, discovered an antigen, which he named My-10, that appears on the surface of immature stem cells but not on the surface of mature cells. [FN6] The patents' specifications disclose a monoclonal antibody, which Civin named anti-My-10, which recognizes the My-10 antigen and is useful in separating stem cells from mature cells. The patents further disclose how a hybridoma which manufactures the anti-My-10 antibody can be produced and note that a sample of the hybridoma has been deposited with the American Type Culture Collection (ATCC), ATCC Accession No. HB-8483, in Rockville, Maryland.

*1708 The '680 and '204 patents claim, respectively, a purified cell suspension of stem cells and

monoclonal antibodies useful in producing such a suspension. The parties do not draw distinctions between the various claims in the patents, and instead premise their arguments as to each patent solely on independent claim 1 of each patent. These claims are set forth below with the disputed limitations from each claim emphasized:

'680 Claim 1: "A suspension of human cells comprising pluripotent lympho- hemopoietic stem cells substantially free of mature lymphoid and myeloid cells."

'204 Claim 1: "A monoclonal antibody which specifically binds to an antigen on nonmalignant, immature human marrow cells, wherein said antigen is stage specific and not lineage dependent, and said antigen is also specifically bound by the antibody produced by the hybridoma deposited under ATCC Accession No. HB-8483. . ." [FN7]

B. CellPro's Activities and Accused Products

1. CellPro's Technology

Four years after the filing date of the parent application of the Civin patents, Dr. Ronald Berenson, a scientist at the Fred Hutchinson Research Center, developed a method of physically separating stem cells from mature cells that was similar to that disclosed in the Civin patents. The monoclonal antibody developed by Berenson for this purpose was designated the 12.8 antibody. [FN8]

Berenson and others at Hutchinson formed CellPro in 1989 and obtained licenses from Hutchinson for the use of Berenson's cell separation technology. In July 1990, CellPro produced, by cloning, a master cell bank constituting 100 vials of 12.8 hybridoma. Some of these vials were subsequently thawed and cloned to create a working cell bank to produce the 12.8 antibody. CellPro began to sell two machines, the Ceprate LC and the Ceprate SC, which its customers used in conjunction with the 12.8 antibody to perform Berenson's cell separation method.

2. CellPro's Knowledge of the Civin Patents and its Procurement of Legal Opinions

At the time CellPro was formed, representatives of CellPro knew of the '680 cell suspension patent, which issued on December 12, 1987. They had also monitored the Official Gazette of the Patent and Trademark Office to determine if Civin had been issued any antibody-related patent; the '204 antibody

patent, which issued on October 23, 1990, was so discovered. See Hopkins II, 978 F. Supp. at 187-88. CellPro does not in fact dispute that it was aware of the existence of the Civin patents when it began its allegedly infringing activity.

Ostensibly concerned that CellPro's activities might fall within the scope of the '680 patent, Thomas Kiley, a member of CellPro's Board of Directors and the company's legal advisor, engaged the law firm of Lyon & Lyon LLP and its partner Coe Bloomberg in early April 1989 to provide an opinion on the validity of the claims of the '680 patent. Bloomberg apparently reported to the CellPro board in May and September 1989 that he had reviewed the prosecution history of the patent and had concluded that the patent was invalid. Bloomberg's oral opinion was first reduced to writing on February 27, 1990. That later written opinion concluded that the claims of the '680 patent were invalid over several pieces of prior art and were unenforceable for inequitable conduct. CellPro used Bloomberg's opinion letter to assist it in raising an additional \$7.5 million from investors. See id.

In the spring of 1991, CellPro's board asked Bloomberg for an opinion concerning the '204 patent. Bloomberg apparently prepared a draft opinion and submitted it to Kiley, who reviewed it and provided Bloomberg with comments. This opinion, like the '680 opinion, concluded that the claims were invalid and unenforceable. Bloomberg also opined that CellPro did not infringe claims 2, 3, 5, and 6, but was silent as to infringement of claims 1 and 4, the claims asserted in this action. The '204 opinion letter was also used by CellPro as a mechanism for inducing investment in the company. In the prospectus accompanying CellPro's public offering, *1709 the company reported that " [b]ased on the advice of Lyon & Lyon, special patent counsel to the company, CellPro believes that [the Civin] patents are invalid and unenforceable." Id. at 189 (internal quotations omitted).

By December of 1991, CellPro had set aside \$3 million as a reserve for potential litigation involving the Civin patents. CellPro also made provision in its financial forecasts for the possibility that it would litigate and lose, and be forced to pay a "stiff royalty" of 15% as damages. Id.

C. The District Court Litigation

1. Infringement

Hopkins, assignee of the Civin patents, and its licensees, Baxter Healthcare and Becton Dickinson, sued CellPro on March 8, 1994, alleging infringement of certain claims of the '204 patent. CellPro, *inter alia*, counterclaimed for a declaratory judgment of invalidity and noninfringement of certain claims of the '680 patent, prompting Hopkins to sue CellPro for infringement of that patent as well. [FN9]

The case was tried to a jury beginning on July 24, 1995. The district court reserved construing the claims until after the presentation of evidence. At that time, the court considered but did not provide the jury with instruction concerning the meaning of the disputed limitations, concluding that the language contained therein could be understood according to its ordinary meaning. See Johns Hopkins Univ. v. CellPro, 894 F. Supp. 819, 827-28 (D. Del. 1995). The jury returned a verdict entirely favorable to CellPro, concluding that all of the asserted claims of both patents were invalid for obviousness and lack of enablement, and that none of the asserted claims was infringed. See Hopkins I, 931 F. Supp. at 307.

Hopkins brought a renewed motion for judgment as a matter of law and in the alternative moved for a new trial, asserting, *inter alia*, that the court had erred in its construction of the disputed claim limitations. The court agreed that its failure to construe the disputed limitations appeared to be in error, see id. at 313, 317, and revisited these and other questions in considering the motion.

a. The '680 Patent

As to the "substantially free" limitation of the '680 claims, the district court, in considering the motion, was "reluctant to impose mathematical certainty on an ambiguous term when [the] patent applicant has strenuously avoided doing so." Id. at 318. However, despite this reluctance, the court adopted a construction that required "a cell suspension of at least 90 purity"; in other words, "the cell suspension must contain no more than 10% patent's disclosure of the production of a stem cell suspension of 90% purity in Table 9." [FN10] See Hopkins I, 931 F. Supp. at 318.

Following its first real construction of the words "substantially free," the court granted Hopkins' motion for judgment as a matter of law on the issue of literal infringement. The court noted that Hopkins could prove infringement without testing the accused cell suspensions, see id. at 319 (citing *1710Allen

Archery, Inc. v. Browning Mfg. Co., 819 F.2d 1087, 1098, 2 USPQ2d 1490, 1498 (Fed. Cir. 1987)), and it summarized the documentary evidence that showed that the cell suspensions produced by CellPro's cell separation technique were of greater than 90% purity. This evidence included a CellPro letter and brochure that explained that CellPro's Ceprate LC device had "achieved purities of 91.5%, 91.6%, and 93.7% during experimental runs of the device." Id. Additionally, a clinical study protocol stated that clinicians had "achieved up to 95% purity during experiments with the Ceprate SC." Id. The court concluded that, in light of this evidence, no reasonable jury could conclude that CellPro did not infringe the asserted claims of the '680 patent. Id.

The court also granted Hopkins' motion for a new trial on the issue of the obviousness of the asserted claims of the '680 patent, see id. at 321; 35 U.S.C. Section 103 (1994), because, *inter alia*, the three references upon which CellPro relied to establish obviousness (viz., Civin, Koeffler, and Amato) were not listed on CellPro's pre-trial order and therefore were not properly before the jury. See Hopkins I, 931 F. Supp. at 320. In its subsequent preparation for the new trial on this issue, CellPro attempted to include evidence showing that the claims as finally construed were either anticipated or obvious in light of a publication by Morstyn. [FN11] The court, however, ruled from the bench that it would not entertain any arguments concerning the Morstyn reference because such arguments were "based on . . . prior art that [CellPro] knew about before the prior trial" but failed to then rely upon. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Oct. 1, 1996) (transcript at 24). [FN12] The court subsequently granted summary judgment of nonobviousness to Hopkins, concluding that CellPro had failed to raise a genuine issue of material fact that warranted a trial on this issue. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Jan. 29, 1997).

b. The '204 Patent

The district court agreed with Hopkins that the "wherein" clause of the '204 claims referred to an antigen that was now more simply understood by those of ordinary skill in the field as the "CD34 antigen," [FN13] and adopted a claim construction that reflected this understanding. Hopkins I, 931 F. Supp. at 314. The court noted that its construction was "unorthodox" because it "defined a large number of words in the claim with reference to a single alphanumeric reference, CD34," but that this

shorthand was warranted in light of the "difficulty of describing the antigen to which the '204 patent refers." Id. at 313. In rejecting CellPro's argument that the court's claim construction should not refer to CD34, but instead My-10, the antigen disclosed in the patent's specification, the court noted that:

Those skilled in the art of making monoclonal antibodies, however, clearly understand that My-10 and CD34 are the same. The attorney prosecuting the application for the '204 patent argued that My-10 was becoming known in the art as CD34 as a result of the International Leukocyte Workshops. The examiner recognized this when she observed that claim 1 "limits the claimed monoclonal antibodies to species that react with a particular antigen (now identified as CD-34)."

Id. at 314. Accordingly, the court concluded that the "wherein" clause was an "attempt to describe a specific physical entity, which those skilled in the art now call the CD34 *1711 antigen," and furthermore that any antibody which binds to this antigen would infringe the asserted claims. Id.

In light of this construction, the court granted Hopkins' motion for a new trial on the issue of literal infringement. The court concluded that " [t]he evidence offered at trial, including [that] through CellPro's own experts, establishes that the 12.8 antibody binds to the CD34 antigen." Id. at 316. Rather than grant Hopkins' renewed motion for judgment as a matter of law, the court at first allowed CellPro to attempt to establish a foundation to support its theories of noninfringement, which mostly hinged upon proof that the 12.8 antibodies bind to mature basophils. See id. at 316, 317. However, the court soon thereafter granted Hopkins' motion for summary judgment on the issue of literal infringement, essentially concluding that the evidence that the 12.8 antibody binds to different species was irrelevant given that it binds to the CD34 antigen. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Nov. 27, 1996).

The court also granted Hopkins' motion for a new trial concerning lack of enablement of the claims of the '204 patent. See Hopkins I, 931 F. Supp. at 322; 35 U.S.C. Section 112, Para. 1 (1994). In support of its defense, CellPro had argued that the specification does not teach one skilled in the art to make antibodies which bind to the CD34 antigen other than the disclosed anti-My-10 antibody, and accordingly that the full breadth of the asserted claims was not enabled. The court disagreed and concluded that:

the weight of the evidence suggests that the '204 patent is enabled. Despite the fact that CellPro's experts claim that the '204 patent is not enabling, none of them can identify anything that is missing from the specification. By contrast, the specification states that Civin's hybridoma is on deposit for others to utilize. In addition, the specification describes the entire fusion process, including the immunogen, which is also on deposit, the specific type of mice immunized, and the use of the methodology utilized by Kohler and Milstein. [FN14]

Hopkins I, 931 F. Supp. at 324. Hopkins subsequently moved for summary judgment. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Feb. 24, 1997). To rebut Hopkins' motion, CellPro offered evidence purporting to show that various experts either could not produce another antibody using the teachings of the patent or otherwise could do so only through undue experimentation. See id.; Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986) (noting that enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly excessive."). The court did not find that CellPro's evidence raised any genuine issue of material fact, and granted Hopkins' summary judgment motion. The court concluded that those "experts" to whom CellPro referred in support of its argument either were not experts, did not follow the teachings of the patent, or otherwise did not engage in undue experimentation. As to those experts that only had success in producing a suitable antibody after several attempts, the court concluded that " [r]outine repetition of a patent's specification to achieve a desired experimental result does not constitute undue experimentation." Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM, at 5 (D. Del. Feb. 24, 1997) (citing PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623-24 (Fed. Cir. 1996)).

CellPro further argued in the district court that the asserted claims of the '204 patent were invalid for failure to satisfy the written description requirement of 35 U.S.C. Section 112, Para. 1 (1994). The court, from the bench, granted CellPro permission to assert this defense, but then granted summary judgment to Hopkins' on the merits. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Oct. 31, 1996) (transcript at 12-13).

*1712 2. Damages and Willful Infringement

With CellPro's liability for infringement decided by the grant of Hopkins' various motions, the issues of damages and willful infringement were tried to a jury beginning March 4, 1997. See Hopkins II, 978 F. Supp. at 186. The jury assessed over \$2.3 million dollars in damages and found CellPro's infringement to be willful. See id. at 191-92. Hopkins then moved for enhanced damages pursuant to 35 U.S.C. Section 284. [FN15] The court, noting that enhanced damages under section 284 are punitive in nature, see, e.g., Beatrice Foods Co. v. New England Printing & Lithographing Co., 923 F.2d 1576, 1580, 17 USPQ2d 1553, 1556 (Fed. Cir. 1991), applied the factors enumerated in Read Corp. v. Portec, Inc., 970 F.2d 816, 827, 23 USPQ2d 1426, 1435-36 (Fed. Cir. 1992), to determine the extent to which enhancement was appropriate. [FN16] Central to the court's decision to treble damages, the maximum enhancement permissible under the statute, was its conclusion that Bloomberg's opinion letters were:

so obviously deficient, one might expect a juror to conclude that the only value they had to CellPro in the world outside the courtroom would have been to file them in a drawer until they could be used in a cynical effort to try and confuse or mislead what CellPro, its Board, and counsel must have expected would be an unsophisticated jury.

Hopkins II, 978 F. Supp. at 193. The district court was not convinced that the opinion letters provided CellPro with a good faith belief that the patents were invalid. See note 16, *supra* (second factor). Specifically, the court found the opinions to be untimely, not competent, and not relied upon by CellPro. See Hopkins II, 978 F. Supp. at 193.

3. The Repatriation Order

As part of the district court's permanent injunction order, Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM (D. Del. Jul. 24, 1997), the court ordered CellPro to repatriate to the United States "all clones or subclones of the 12.8 hybridoma cell line previously exported by it, as well as any further clones or subclones produced therefrom," and any antibodies produced therefrom. Id. at 3-4. This order encompassed six vials of 12.8 hybridoma from CellPro's United States cell bank which CellPro sent to its Canadian business partner, Biomira, Inc., and cloned vials and antibodies produced therefrom in Canada. These six vials, like the other vials in the cell bank, were created prior to the issuance of the '204

patent, the only patent that is relevant to the 12.8 hybridoma, but were sent to Canada during the term of that patent. The six vials were never thawed or used in any manner prior to their export. One of the six vials was cloned in Canada to produce a working Canadian cell bank of 32 vials of 12.8 hybridoma. Under CellPro's contract with Biomira, Biomira thawed and used the hybridoma from the Canadian cell bank to make 12.8 antibodies for the performance of the Berenson cell separation technique in Canada. Title to the hybridoma, however, remained with CellPro.

In its memorandum opinion supporting its repatriation order, the court did not find compelling CellPro's argument that none of its activities concerning the six vials exported to Canada were infringing uses under 35 U.S.C. Section 271 and that they were thus free of the court's equitable power to order repatriation:

CellPro argues that because it shipped cells that were part of the original batch of noninfringing cells -- rather than those that were cloned [after the issuance of the '204 patent in the United States] -- it did not run afoul of Section 271(a). The court finds this distinction to be immaterial. CellPro created the 12.8 hybridoma with the intention of developing a bank of identical cells to produce a monoclonal antibody--the 12.8 antibody. Thus, by using some cells in the [United States cell] bank for the purpose of cloning or testing, it is committing an infringing "use" with respect to the bank as a whole.

Accordingly, because CellPro created and maintained its hybridoma in Canada as a result of infringing activities in the United States, the court finds that it will be acting within its equitable powers under 35 U.S.C. Section 283 by ordering CellPro to repatriate *1713 the hybridomas stored at Biomira. Doing so would tend to reestablish the status quo as it existed before CellPro willfully infringed the asserted claims of the '204 patent.

Id. at 27 (memorandum opinion).

CellPro appealed numerous points of error to this court. We have jurisdiction pursuant to 28 U.S.C. Section 1295(a)(1) (1994).

DISCUSSION

A. Standard of Review

Judgment as a matter of law (JMOL) is appropriate

when "a party has been fully heard on an issue and there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue." Fed. R. Civ. P. 50(a)(1). We review a district court's decision on a motion for JMOL de novo, reapplying the JMOL standard. See Markman v. Westview Instruments, Inc., 52 F.3d 967, 975, 34 USPQ2d 1321, 1326 (Fed. Cir. 1995) (in banc), aff'd, 517 U.S. 370, 38 USPQ2d 1461 (1996). Summary judgment is appropriate when there are no genuine issues of material fact and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c). We similarly review a district court's grant of summary judgment de novo, reapplying the summary judgment standard. See Conroy v. Reebok Int'l, Ltd., 14 F.3d 1570, 1575, 29 USPQ2d 1373, 1377 (Fed. Cir. 1994).

" [T]he determination whether a claim has been infringed requires a two-step analysis: First, the claim must be properly construed to determine its scope and meaning. Second, the claim as properly construed must be compared to the accused device or process." Carroll Touch, Inc. v. Electro Mechanical Sys., Inc., 15 F.3d 1573, 1576, 27 USPQ2d 1836, 1839 (Fed. Cir. 1993). The first step, claim construction, is a question of law, which we review de novo. See Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456, 46 USPQ2d 1169, 1174 (Fed. Cir. 1998) (in banc). The second step is factual. See North Am. Vaccine, Inc. v. American Cyanamid Co., 7 F.3d 1571, 1574, 28 USPQ2d 1333, 1335 (Fed. Cir. 1993). When construing a claim, a court principally consults the evidence intrinsic to the patent, viz., the claims themselves, the written description portion of the specification, and the prosecution history. See Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582-83, 39 USPQ2d 1573, 1576-77 (Fed. Cir. 1996). Whether making and using an invention would have required undue experimentation, and thus whether a disclosure is enabling under 35 U.S.C. Section 112, Para. 1 (1994), is a legal conclusion based upon underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736- 37, 8 USPQ2d 1400, 1402 , 1404 (Fed. Cir. 1988).

Because courts have broad discretion in determining the scope of injunctive relief under 35 U.S.C. Section 283 (1994), we review the scope of a district court's permanent injunction for an abuse of discretion. See Ortho Pharm. Corp. v. Smith, 959 F.2d 936, 945, 22 USPQ2d 1119, 1127 (Fed. Cir. 1992). Likewise, the propriety of an evidentiary ruling by the district court is reviewed for an abuse of discretion. See Kearns v. Chrysler Corp., 32 F.3d 1541, 1547, 31 USPQ2d

1746, 1750 (Fed. Cir. 1994); In re Merritt Logan, 901 F.2d 349, 359 (3rd Cir. 1990).

Whether infringement was willful is a question of fact, and we will not reverse a jury determination on this issue unless it was unsupported by substantial evidence. See Hoechst Celanese Corp. v. BP Chems. Ltd., 78 F.3d 1575, 1583, 38 USPQ2d 1126, 1132 (Fed. Cir. 1996). A district court's decision to enhance damages for willful infringement and the extent of the enhancement is reviewed for an abuse of discretion. See SRI Int'l, Inc. v. Advanced Tech. Labs., Inc., 127 F.3d 1462, 1468, 44 USPQ2d 1422, 1427 (Fed. Cir. 1997).

B. Validity and Infringement of the '680 Patent

1. Claim Construction and Infringement

CellPro asserts that the district court's construction of the "substantially free" limitation to require no more than 10% mature cells was in error. Instead CellPro believes that this limitation should be construed to mean an immeasurable amount of mature cells. Accordingly, CellPro contends that JMOL of infringement was erroneously granted, because cell suspensions produced by its technique and equipment contained measurable amounts of mature cells numbering in the "millions."

To support its claim construction, CellPro points to the prosecution history of the '680 patent, which progressed in relevant part as follows: The examiner rejected the claims as anticipated by two prior art publications by Bodger et al. The applicant responded by noting that Bodger's antibodies could not be used to produce a cell suspension that was "substantially free" of mature cells as required by the claim language. The examiner was not persuaded and noted that " [t]he metes and bounds of 'substantially free' have not been established" by the applicant, to which the applicant responded:

*1714 "Substantially free" is defined by its plain meaning and further by the stated characteristics of the anti-My-10 antibody At page 5, lines 27-31, of the specification [see '680 patent, col. 6, ll. 62-67] it is explicitly stated, "Various assay techniques have been employed to test for the presence of the My-10 antigen, and those techniques have not detected any appreciable number (i.e., not significantly above background) of normal, mature human myeloid and lymphoid cells in My-10-positive populations." For example, when My-10+ cells are incubated with a series of monoclonal antibodies which react with T-

lymphocytes [i.e., a type of mature cell], no cells are found to be reactive. Thus, by the means presently available to the art, no T-lymphocytes are found in My-10+ cell populations.

(emphasis in original). [FN17] The applicant also noted that "Bodger's cell population has some T-cells present, but [that] the present invention has none," and therefore that Bodger's cell suspension would be ineffective in preventing GVHD.

Hopkins responds that the district court's claim construction was correct and was consistent with the intrinsic evidence. Hopkins notes that the specification, reflecting the imperfect state of the art and specifically the imperfect nature of cell separation techniques such as the FACS method, teaches that the disclosure concerning preparation of antibodies would enable the creation of only "relatively pure" stem cell suspensions. See '680 patent, col. 4, ll. 55. Hopkins asserts that the highest disclosed purity for a stem cell suspension created by the disclosed technique, viz. 90%, see '680 patent, col. 18, tbl. 9, should define the outer bounds of the words "substantially free." Hopkins argues that CellPro's proposed claim construction and citation from the prosecution history are inconsistent with Table 9, which describes small but measurable amounts of mature cells.

[1] We agree with Hopkins that the district court's construction of the words "substantially free" was not in error. Table 9, the only disclosed embodiment of the claimed cell suspension, [FN18] is highly indicative of the scope of the claims. A patent claim should be construed to encompass at least one disclosed embodiment in the written description portion of the patent specification. This maxim flows from the statutory requirement that " [t]he specification shall contain a written description of the invention," 35 U.S.C. Section 112, Para. 1 (1994), which requires a patent applicant to disclose in the specification sufficient subject matter to support the breadth of his claim. See Specialty Composites v. Cabot Corp., 845 F.2d 981, 987, 6 USPQ2d 1601, 1604 (Fed. Cir. 1988) (noting that what is patented "is defined by the words in the claims if those claims are supported by the specification in the manner required by 35 U.S.C. Section 112."); Pall Corp. v. Micron Separations, Inc., 66 F.3d 1211, 1219, 36 USPQ2d 1225, 1230-31 (Fed. Cir. 1995). A claim construction that does not encompass a disclosed embodiment is thus "rarely, if ever, correct and would require highly persuasive evidentiary

support." Vitronics, 90 F.3d at 1583, 39 USPQ2d at 1578. Accordingly, CellPro's claim construction, that the cell suspension of the claims can contain only an immeasurable amount of mature cells, is undermined by Table 9 of the specification, which describes the only embodiment of the invention disclosed in the specification and discloses a cell suspension that contains 3% mature neutrophils, 6% mature monocytes, and 1% mature lymphocytes, all of which constitute measurable quantities of mature lymphoid cells. See '680 patent, col. 18, tbl. 9 n.*.

CellPro also notes that in response to the examiner's request to clarify the "metes and bounds" of the words "substantially free," the applicant, quoting the specification, noted that " [v]arious assay techniques have been employed to test for the presence of the My-10 antigen, and those techniques have not detected any appreciable number (i.e., not significantly above background) of normal, mature human myeloid and lymphoid cells in My-10-positive populations." However, this passage does not describe the purity of a cell suspension produced by the disclosed technique, but rather describes the various species of cells that are present in "My-10-positive populations," i.e., in populations which express the My-10 antigen. Thus, the quoted passage merely clarifies that a population of cells expressing the *1715 My-10 antigen contains no "appreciable number" of mature cells; it does not support the inference that such a population, when included with other mature cells and sorted according to the technique disclosed in the '680 patent, can be sorted to recover only My-10-positive cells. Not only is this inference directly contrary to the reality of the cell suspension disclosed in Table 9, but it is also contrary to the expert testimony at trial which established that sorting techniques such as FACS suffer from "practical limitations" and are capable of producing cell suspensions of only 85-90% purity, the upper value of which is consistent with the district court's construction. See Hopkins I, 931 F. Supp. at 318. Moreover, the record is silent concerning the expected background levels for mature cells in a sorted cell suspension. Thus, reference to "background level" sheds little light on the construction of the words "substantially free."

CellPro next calls attention to the prosecution history in which the applicant notes that "when My-10+ cells are incubated with a series of monoclonal antibodies which react with T-lymphocytes, no cells are found to be reactive." Like the portion of the prosecution history cited above, this statement does

not address the purity of a suspension produced by separation.

Finally, the applicant's statement that "Bodger's cell population has some T- cells present, but the present invention has none" does not support CellPro's proffered construction. That the inventive cell suspension might contain no (or an immeasurable amount of) T-cells does not mean that the cell suspension does not contain measurable amounts of other mature myeloid and lymphoid cells. Table 9 illustrates this point. Mature lymphocytes, of which T-cells are a subset, constituted a mere 1% of the stem cell suspension. However, other mature cells, including neutrophils (3%) and monocytes (6%), were also present in the suspension. See note 10, *supra*. In the end, it is unremarkable that the claims issued over Bodger, a reference which disclosed the use of an antibody that, unlike My-10, was specifically reactive with T-cells and consequently produced a cell suspension that was not substantially free of mature lymphoid cells. [FN19]

Thus, none of the statements in the prosecution history that CellPro cites constitutes "highly persuasive" evidence to suggest that we should deviate from a claim construction that is required in order to encompass the only disclosed embodiment of a cell suspension in the '680 patent. We therefore affirm the district court's construction of the language "substantially free of mature lymphoid and myeloid cells" as requiring no more than 10% mature lymphoid and myeloid cells and its grant of JMOL in favor of Hopkins on the issue of literal infringement.

2. Obviousness/Anticipation

CellPro argues that it was error for the court, after granting Hopkins' motion for a new trial on the issue of obviousness, to exclude the Morstyn reference as evidence of obviousness. CellPro asserts that it should not be held to have "waived" its right to rely on the Morstyn reference simply because it knowingly chose not to rely on Morstyn during the first trial. CellPro argues that Morstyn, which CellPro characterizes as enabling one of ordinary skill in the art to produce a stem cell suspension of 90% purity, did not become pertinent until after the first trial when the court adopted its "broadened" construction of the words "substantially free." CellPro asserts that Morstyn, alone or in combination with Beverley, raises a genuine issue of material fact concerning the validity of the claims of the '680 patent and should have precluded summary judgment in favor of Hopkins on the issue of obviousness. Hopkins

responds that CellPro waived its right to subsequently rely on Morstyn by virtue of its failure to include Morstyn in the final pretrial order pursuant to Fed. R. Civ. P. 16(e). [FN20] Thus, according to Hopkins, the district court did not err in failing to consider invalidity arguments premised upon Morstyn.

[2] We agree with CellPro that the district court erred in failing to consider CellPro's Morstyn-based invalidity challenge. The district court, when it construed the claims after trial, changed the rules of the game. Specifically, when the court rendered its claim construction of the words "substantially free" to encompass cell suspensions of at least 90% purity, new prior art became potentially relevant to the validity of those claims. CellPro was entitled to present this *1716 new art following the court's grant of Hopkins' new trial motion so that Morstyn could be evaluated on its merits. That CellPro knew of Morstyn before the first trial but chose not to rely upon it then cannot constitute a waiver to apply that art against a claim whose construction was not yet finally determined by the court.

Our conclusion is not altered by Hopkins' "pretrial order" argument, because this argument has no merit. Nothing in Rule 16(e) indicates that a pretrial order from a first trial controls the range of evidence to be considered in a second trial. Indeed, such a cramped interpretation of Rule 16(e) would greatly hobble the parties from meaningfully relitigating an issue which the court has decided required retrial under Rule 59.

Accordingly, the court erred in determining that CellPro had waived its right to rely on the Morstyn reference to establish that the claims of the '680 patent were either anticipated or would have been obvious to one of ordinary skill. [FN21] We therefore vacate and remand so that the Morstyn reference can be considered on its merits. [FN22]

C. Validity and Infringement of the '204 Patent

1. Claim Construction and Infringement

CellPro asserts that the district court erred in construing the "wherein" clause of the '204 patent as referring to "the CD34 antigen." CellPro contends that reference to "the CD34 antigen" was unnecessary and incorrect: it was unnecessary because the "wherein" clause clearly refers to a single antigen, the My-10 antigen, that is disclosed in the specification; it was incorrect, CellPro continues, because "CD34" refers to a genus of antigens and thus erroneously sweeps into the claims all CD34 antibodies,

regardless whether they bind to the My-10 antigen. CellPro states that what the scientific community refers to as "the CD34 antigen" is in fact "a collection of different molecules, all based on the same protein backbone, [with] a number of molecular forms." CellPro's Opening Brief at 32 (quoting its expert's declaration). Apparently CellPro considers these different molecules to be different antigens, because it explains that its 12.8 antibody binds to "a CD34 antigen" that is different from My-10. CellPro's Reply Brief at 13 (emphasis added).

Significantly, Hopkins agrees with CellPro that the claims cover a single antigen, not a genus of antigens, but contends that "the CD34 antigen" is an apt description of that claimed antigen. In support of its position, Hopkins points, *inter alia*, to the prosecution history. Specifically, Hopkins highlights the applicant's reference during prosecution to the conclusion of the Third International Workshop on Leukocyte Differentiation ("Workshop") and the applicant's statement to the examiner that "[t]he antigen recognized by the monoclonal antibodies of this invention has been designated My-10 . . . by the inventor, and subsequently CD-34 (antibody cluster designation) by the [Workshop]." The Workshop's report, also submitted by the applicant to the examiner, describes the antigen to which anti-My-10 is bound as "the CD34 antigen." [FN23] In support of the district court's grant of summary judgment of infringement, Hopkins points to several other pieces of documentary evidence in which CellPro admits either that its 12.8 antibody binds to "the CD34 antigen" or otherwise binds to the same antigen as anti-My-10. Thus, Hopkins contends that CellPro infringes the claims regardless of whether the antigen of the claims is referred to as "the CD34 antigen," "My-10," or (to paraphrase the "wherein" clause) "the antigen bound by the antibody produced by the hybridoma on deposit."

[3] We agree with Hopkins that the district court's claim construction was not in error. The district court may have been correct that it was "unorthodox" to condense the meaning of the "wherein" clause into the simpler language of "the CD34 antigen." However, this treatment was not erroneous, as Hopkins' citations from the prosecution history show; the applicant directly equated My- 10 and thereby the entirety of the "wherein" clause with what the scientific *1717 community had come to understand as "the CD34 antigen." Furthermore, the record makes clear that the term "the CD34 antigen" is synonymous with the antigen discovered by Civin.

CellPro cites no intrinsic evidence and no credible extrinsic evidence in support of its theory that "the CD34 antigen" encompasses a genus of antigens. Instead, what the evidence does show is that the CD34 antigen contains a number of epitopes [FN24] on its surface to which the various CD34 antibodies can bind. For example, the Workshop report explains that the various CD34 antibodies known as of that date all bind to the CD34 antigen, but to different epitopes, Joint App. at EA7275-82, and one study concluded that "at least three distinct CD34 epitopes" were expressed on the surface of the CD34 antigen, *id.* at EA7283. The same conclusion is confirmed by CellPro's own internal documents. For example, Dr. Berenson concluded that "[Antibody 12.8] recognizes the same antigen as does [anti-]My-10 Unlike [anti-My-10], antibody 12.8 recognizes a distinct epitope that is also present on a similar population of marrow cells in nonhuman primates." *Id.* at A1390. Other evidence supports the conclusion that 12.8 and anti-My-10 bind to the same antigen, see *id.* at A5846 (testimony of CellPro's expert, Dr. D.R. Sutherland) ("So collectively we think that this data suggests that the [anti-] My-10 and 12.8 binding sites are distinct and nonoverlapping binding sites on the CD34 molecule."); *id.* at EA5462 (Bloomberg '204 opinion letter) ("It is our understanding, based upon discussions with CellPro scientists, that the monoclonal antibody used by CellPro does not bind to the same epitope in the My-10 antigen as does the Civin anti-My-10 monoclonal antibody."), and that this antigen is the CD34 antigen, see *id.* at EA3781 (CellPro's FDA filing) ("The primary reagent is a monoclonal antibody (Mab) 12.8 which specifically binds to a unique antigen (CD34) on the target cells (stem cells).").

CellPro cites no evidence to refute the clear conclusion to be drawn from these documents that its 12.8 antibody binds to the CD34 antigen, albeit to a different epitope than does the anti-My-10 antibody disclosed in the patent, and therefore literally infringes the claims of the '204 patent. Accordingly, the district court's construction of the "wherein" clause and its subsequent grant of summary judgment of infringement are affirmed.

2. Enablement

CellPro argues that the claims of the '204 patent, which both parties agree are drawn to the genus of antibodies which bind to the claimed antigen, are not enabled as required by 35 U.S.C. Section 112, Para.

1, and that the district court erred in granting summary judgment to the contrary. CellPro contends that the patent discloses only the method of producing the anti-My-10 antibody and is therefore insufficient to enable one of ordinary skill in the art to make and use the broader genus of claimed antibodies. See, e.g., Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) ("To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.") (citation and quotation omitted). In support, CellPro points to evidence that it believes conclusively shows that one of ordinary skill following the techniques disclosed in the patent could produce other antibodies only after undue experimentation, and contends that this evidence should have precluded summary judgment.

Hopkins responds that the patent's disclosed method of producing antibodies, the Kohler/Milstein method, has been used to produce over forty additional CD34 antibodies, and that most of these antibodies, including CellPro's 12.8 antibody, see Hopkins I, 931 F. Supp. at 323, were produced using the disclosed preferred immunogen, the KG-1a cell line. See note 14, *supra* (outlining the Kohler/Milstein method); '204 patent, col. 3, ll. 41-50 & col. 5, ll. 30-47. [FN25] Hopkins further asserts that CellPro's evidence of undue experimentation is insufficient to preclude entry of summary judgment.

*1718 When ruling on Hopkins' motion for summary judgment of enablement, the district court was obliged to have viewed the evidence in the light most favorable to the nonmoving party, in this case CellPro, and to have resolved any evidentiary doubts in CellPro's favor. See C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc., 991 F.2d 670, 672, 15 USPQ2d 1540, 1542 (Fed. Cir. 1990). Moreover, the court must have "view [ed] the evidence presented through the prism of the substantive evidentiary burden" that would inhere at trial. Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 254 (1986). This burden rested upon CellPro, who had to prove by clear and convincing evidence facts establishing a lack of enablement. See Morton Int'l Co. v. Cardinal Chem. Co., 5 F.3d 1464, 1469, 28 USPQ2d 1190, 1194 (Fed. Cir. 1993); 35 U.S.C. Section 282 (1994). However, CellPro's evidence must have done more than simply raise some doubt regarding enablement: "If the evidence is merely colorable, or is not significantly probative, summary judgment may be granted." Anderson, 477 U.S. at 249-50 (citations omitted). Instead, CellPro's evidence must have

shown that a material factual dispute existed, i.e., a dispute upon which a reasonable jury could have resolved enablement in CellPro's favor after a review of the entire record. See Sweats Fashions, Inc. v. Pannill Knitting Co., 833 F.2d 1560, 1562, 4 USPQ2d 1793, 1795 (Fed. Cir. 1987).

[4] Our review of the entire record leads to the conclusion that CellPro failed to raise a genuine issue of material fact concerning enablement, and therefore that the district court did not err in granting summary judgment. We consider each piece of CellPro's evidence in turn.

CellPro first contends that Civin's laboratory never again succeeded in producing another CD34 antibody using the technique disclosed in his patent specification despite a "major effort" on his part to do so. However, as the district court noted upon granting Hopkins' motion for a new trial on enablement, CellPro failed to offer evidence that many of those working on projects in Civin's lab, including undergraduate students or others who had never before made a monoclonal antibody, were of ordinary skill in the art. [FN26] Hopkins I, 931 F. Supp. at 323. Despite being warned of this evidentiary shortcoming, CellPro thereafter apparently produced no evidence concerning the level of skill of those individuals working under Civin's supervision. See Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-RRM, at 5. Because it is imperative when attempting to prove lack of enablement to show that one of ordinary skill in the art would be unable to make the claimed invention without undue experimentation, see *Genentech, supra*, CellPro's evidence concerning Civin's subsequent work is insufficient as a matter of law.

CellPro next contends that the testimony of its expert, Dr. D.R. Sutherland, raises a genuine issue of material fact concerning enablement. Sutherland testified that he was unsuccessful in making a CD34 antibody. However, and as the district court noted upon granting Hopkins' motion for a new trial, Sutherland "did not use the screening technique disclosed in the specification" for identifying suitable hybridomas. Hopkins I, 931 F. Supp. at 323. A party who wishes to prove that the claims of a patent are not enabled by means of a failed attempt to make the disclosed invention must show that the patent's disclosure was followed. Because Sutherland deviated from the teachings of the patent in his failed attempts to make the claimed antibodies, his testimony is insufficient to disprove enablement as a matter of law. [FN27]

CellPro also cites the expert declaration of Dr. John Wijdenes in an attempt to prove that the amount of experimentation needed to successfully practice the invention disclosed in the '204 patent was undue. Although Wijdenes concluded that it was generally "more difficult" for him to produce a CD34 antibody than other monoclonal antibodies, he did not attribute this difficulty to any shortcomings in the disclosure of the '204 patent. Instead, Wijdenes's declaration suggests that the Kohler/Milstein technique was not foolproof, and that success with this technique commonly required repetition. *1719 This lack of certainty was thus not attributable to a failure of disclosure in the '204 patent. Such routine experimentation does not constitute undue experimentation:

The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.

PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996) (quotation and citation omitted); see also In re Wands, 858 F.2d 731, 736-40, 8 USPQ2d 1400, 1403-07 (Fed. Cir. 1988) (applying this principle in the context of monoclonal antibody production). Furthermore, Wijdenes explained that the relative difficulty that was encountered in producing CD34 antibodies may have been due to the weak immunogenicity of the KG-1a cell line, see Joint App. at A23360, not because of an insufficiently enabling disclosure. In any event, Wijdenes was able to produce six CD34 antibodies using the KG-1a immunogen, see id. at A23361, and he noted that seven other CD34 antibodies were successfully manufactured using the KG-1 immunogen, see id. at A23343, [FN28] which, if anything, suggests that the disclosure of those immunogens in the patent was sufficient to enable those of ordinary skill to produce a host of CD34 antibodies. [FN29]

CellPro finally contends that no one ever succeeded in making CD34 antibodies using either purified My-10+ cells or immuno-precipitated My-10 antigens as the immunogens in the Kohler/Milstein method. See Hopkins I, 931 F. Supp. at 323. Hopkins argues that this fact, even if true, is legally irrelevant because the

use of these immunogens was disclosed in the patent specification as alternatives to the preferred use of the KG-1/KG-1a cell line. See '204 patent, col. 5, l. 65 to col. 6, l. 27. Hopkins is correct; CellPro can carry its burden only by showing that all of the disclosed alternative modes are insufficient to enable the claims, because "[t]he enablement requirement is met if the description enables any mode of making and using the invention." Engel Indus., Inc. v. Lockformer Co., 946 F.2d 1528, 1533, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991). CellPro's silence concerning enablement by use of the KG-1/KG-1a cell lines makes its argument on this point specious.

In conclusion, our consideration of the record makes clear that CellPro has not raised a genuine factual dispute concerning the enablement of the claims of the '204 patent. We therefore affirm the district court's grant of Hopkins' summary judgment motion on this issue.

3. Written Description

CellPro also asserts that the claims of the '204 patent are invalid under Section 112, Para. 1, because they lack an adequate written description. Specifically, CellPro relies on Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997), cert. denied, 118 S. Ct. 1548 (1998), which held that a genus of vertebrate or mammalian insulin cDNA was not adequately described by the patent's disclosure of a single species of rat insulin cDNA. CellPro argues by analogy that the claims of the '204 patent are invalid because they disclose only a single antigen and antibody. Hopkins responds that this court should not entertain CellPro's written description challenge because CellPro did not present it to the district court and therefore cannot raise it for the first time on appeal.

We agree with Hopkins. Our review of the record shows that CellPro's written description argument in the district court was premised on the argument that the claims of the '204 patent would encompass monoclonal antibodies that bind to antigens on mature cells, but that the written description did not describe this aspect of the invention and in fact expressly disclaimed an invention of such broad scope. See Joint App. at A19087.5, A19296-98. This is not the Lilly-based written description argument that CellPro currently asserts on appeal.

CellPro also cites a document that it filed in the district court (only one page of which is included in

the appendix filed in this court) in support of its contention that it raised a Lilly-based challenge in the district court. See Joint App. at A18371. However, in that page, CellPro merely mentioned the "genus-species" problem addressed by Lilly in a footnote; it did not make a serious Lilly-based *1720 argument as an alternative to its argument that the claims erroneously encompassed antibodies that bound to mature cells. Moreover, the main purpose of the document was to argue that the sufficiency of a written description under Section 112, Para. 1, is a question of fact. As a general rule, an appellate court will not hear on appeal issues that were not clearly raised in the proceedings below. See Singleton v. Wulff, 428 U.S. 106, 120 (1976); Braun, Inc. v. Dynamics Corp. of Am., 975 F.2d 815, 821, 24 USPQ2d 1121, 1126 (Fed. Cir. 1992). This rule ensures that "parties may have the opportunity to offer all the evidence they believe relevant to the issues . . . [and] in order that litigants may not be surprised on appeal by final decision there of issues upon which they have had no opportunity to introduce evidence." Hormel v. Helvering, 312 U.S. 552, 556 (1941). CellPro's casual reference in a footnote was insufficient to place its Lilly-based written description argument in issue before the district court. We therefore decline to address the merits of this argument on appeal.

D. Willful Infringement/Enhanced Damages

CellPro argues several points of error relevant to the district court's decision to treble damages. We consider each of these arguments in turn, but are not persuaded that any reversible error has occurred.

CellPro contends that the jury's finding of willfulness cannot stand because it is premised upon two errors committed by the district court. CellPro first asserts that the court erred in excluding from the jury evidence that CellPro had been wholly successful in the first trial, evidence that CellPro argues bears on the reasonableness of its actions. CellPro states that the test for willful infringement is "whether, under all the circumstances, a reasonable person would prudently conduct himself with any confidence that a court might hold the patent invalid or not infringed." State Indus., Inc. v. Mor-Flo Indus., Inc., 883 F.2d 1573, 1581, 12 USPQ2d 1026, 1032 (Fed. Cir. 1989), and that its vindication in the first trial is part of the "totality" of the evidence that should have been considered in a proper willfulness determination. See, e.g., Studiengesellschaft Kohle v. Dart Indus., Inc., 862 F.2d 1564, 1573, 9 USPQ2d 1273, 1282 (Fed. Cir. 1988) (noting that willful

infringement can be found "only after due consideration of the totality of the circumstances"). Hopkins responds that the prior jury verdict is irrelevant because, *inter alia*, it was rendered in 1995, at least four years after CellPro learned of the Civin patents and thereafter continued to infringe. Alternatively, Hopkins contends that even if the prior verdict was relevant, the court had discretion under Fed. R. Evid. 403 to exclude it because the potential for unfair prejudice and confusion that might have resulted from the jury's consideration of this erroneous verdict outweighed the probative value of the fact of the verdict.

[5] We agree with Hopkins that the district court did not abuse its discretion in excluding the existence of the prior liability verdict from the subsequent trial on willfulness and damages. First, as Hopkins notes and CellPro does not dispute, CellPro had notice of the '680 patent by 1989 and the '204 patent by 1991. Because such notice placed upon CellPro on those dates the duty to exercise due care to determine whether or not it was infringing, see, e.g., Kloster Speedsteel AB v. Crucible, Inc., 793 F.2d 1565, 1579, 230 USPQ 81, 90 (Fed. Cir. 1986), they were the proper times for assessing CellPro's willfulness. See, e.g., Datascope Corp. v. SMEC, Inc., 879 F.2d 820, 828-29, 11 USPQ2d 1321, 1327 (Fed. Cir. 1989).

[FN30] The 1995 jury verdict had no bearing upon the willfulness of CellPro's infringement on the dates it received notice of Hopkins' patent rights. Moreover, we agree with Hopkins that consideration of the 1995 jury verdict, which was ultimately determined to be premised upon an erroneous claim construction, had significant potential to confuse the jury. Cf. Texas Instruments v. Cypress Semiconductor Corp., 90 F.3d 1558, 1569 n.11, 39 USPQ2d 1492, 1502 n.11 (Fed. Cir. 1996) (upholding exclusion of the ITC's non-binding claim construction from a *1721 subsequent district court jury). In sum, we conclude that CellPro has not met its burden of showing that the district court abused its discretion in excluding the fact of the 1995 liability verdict from the willfulness jury.

CellPro also argues that the jury's willfulness finding cannot stand because the jury instructions erroneously mandated the jury to find that its infringement had been willful. CellPro points to the statements in the instructions to the effect that "no reasonable jury" could fail to find either that CellPro infringed the '680 and '204 patents or that these patents were valid. CellPro contends that these

statements, coupled with the court's subsequent definition of willful infringement, i.e., "that the infringer had no reasonable basis for believing it had a right to engage in the infringing acts," forced a finding of willful infringement, because, according to CellPro, if no reasonable juror could have reasonably found the patents invalid or not infringed, it would likewise necessarily have been unreasonable for CellPro to have had such a belief.

[6] We do not accept CellPro's argument. That no reasonable jury could fail to find that CellPro infringed valid patents says nothing about CellPro's willfulness, a determination which is reflective of an infringer's culpability. See Rite-Hite Corp. v. Kelley Co., 819 F.2d 1120, 1126, 2 USPQ2d 1915, 1919 (Fed. Cir. 1987) ("The term 'willfulness' thus reflects a threshold of culpability in the act of infringement. . . ."). The district court's statements concerning infringement and validity were properly designed to ensure that the willfulness jury didn't collaterally consider CellPro's liability for infringement in its deliberations. Prior to its instructions on willful infringement, the district court summarized the statements of which CellPro complains as follows:

The Court thus determined that both the '204 and '680 patents are valid and infringed by CellPro. Accordingly, there are no issues for you to decide concerning CellPro's liability for infringement of the '204 and '680 patents. In your deliberations you are bound to accept my determination that CellPro infringes these two patents, and that both patents are valid.

Joint App. at A26767. The jury instruction only separated considerations of liability and willfulness; we discern no error in that instruction.

CellPro next asserts that the court erred in failing to grant its renewed JMOL motion concerning willfulness. CellPro contends that a reasonable jury, upon consideration of its evidence, could not have found that its infringement was willful. Hopkins responds that the jury's finding of willfulness was supported by substantial evidence.

Willfulness is a question of fact to be proven by clear and convincing evidence. See SRI Int'l, Inc. v. Advanced Tech. Labs., Inc., 27 F.3d 1462, 1465, 44 USPQ2d 1422, 1424 (Fed. Cir. 1997) (noting that the "clear and convincing" evidentiary standard is appropriate because "the boundary between unintentional and culpable acts is not always bright,"

" quoting Pall Corp. v. Micron Separations, Inc., 66 F.3d 1211, 1221, 36 USPQ2d 1225, 1232 (Fed. Cir. 1995)). Because CellPro had knowledge that it might infringe the Civin patents, it had an affirmative duty to exercise due care to avoid infringement. See SRI, 27 F.3d at 1464, 44 USPQ2d at 1423. CellPro attempted to discharge this duty by procuring legal opinions concerning the validity of the Civin patents and its infringement thereof. See Read Corp. v. Portec, Inc., 970 F.2d 816, 828, 23 USPQ2d 1426, 1437 (Fed. Cir. 1992) (noting that the duty to avoid infringement "normally entails obtaining advice of legal counsel although the absence of such advice does not mandate a finding of willfulness"). Our case law makes clear that legal opinions that conclude (even if ultimately incorrectly) that an infringer would not be liable for infringement may insulate an infringer from a charge of willful infringement if such opinions are competent (and followed). An opinion is competent if it is "thorough enough, as combined with other factors, to instill a belief in the infringer that a court might reasonably hold the patent is invalid, not infringed, or unenforceable." Ortho Pharm. Corp. v. Smith, 959 F.2d 936, 944, 22 USPQ2d 1119, 1126 (Fed. Cir. 1992).

[7] Substantial evidence supports the district court's conclusion that a reasonable jury could have concluded that the opinion letters were not adequate to defeat a finding of willfulness. Kiley, the CellPro representative who procured the opinion letters from Bloomberg, was highly sophisticated in matters of patent law and in the involved technology. Kiley had worked as a patent examiner and later was a partner at the law firm of Lyon & Lyon, where he handled patent prosecution and patent litigation. See Hopkins II, 978 F. Supp. at 187. It is therefore reasonable to conclude that Kiley should have been on notice concerning the opinions' *1722 obvious shortcomings and accordingly of the impropriety of CellPro's course of action. See, e.g., Underwater Devices, Inc. v. Morrison-Knudsen Co., 717 F.2d 1380, 1390, 219 USPQ 569, 576 (Fed. Cir. 1983). The opinions did not attempt to link the disclosures of the prior art references relied upon to establish anticipation or obviousness with the limitations of the claims of the patents. For example, and as the district court recognized, none of the allegedly anticipatory references cited in the '680 opinion letter even refers to a cell suspension. See Hopkins II, 978 F. Supp. at 194. The '204 opinion letter concluded that CellPro did not infringe claims 2, 3, 5, and 6 of the '204 patent, but conspicuously omitted any

reference to claims 1 and 4, the claims asserted by Hopkins in this action. Further, the opinion letters are merely conclusory as to their allegations concerning inequitable conduct, and importantly make no mention that intent to deceive is a necessary component of this defense, a fact that is often difficult to establish. See Kingsdown Med. Consultants, Ltd. v. Hollister, Inc., 863 F.2d 867, 9 USPQ2d 1384 (Fed. Cir. 1988) (in banc). Such shortcomings should have been especially troublesome to a knowledgeable practitioner like Kiley, especially considering that the opinions did not express an opinion concerning infringement of the broadest claims. Further suspicion concerning CellPro's good faith exists in the record, but we find it unnecessary to summarize such evidence here. Under the circumstances, we cannot say that a reasonable jury could not have concluded that the opinion letters were ineffective to instill in CellPro, through Kiley, reasonable confidence that its activities did not infringe valid patents.

CellPro's final argument on willfulness is that the district court abused its discretion in deciding to treble Hopkins' damages under 35 U.S.C. Section 284. Although Section 284 does not state a basis upon which a district court may increase damages, it is well established that enhancement of damages may be premised upon a finding of willful infringement. See, e.g., Beatrice Foods Co. v. New England Printing & Lithographing Co., 923 F.2d 1576, 1578, 17 USPQ2d 1553, 1555 (Fed. Cir. 1991). However, a finding of willful infringement does not mandate that the district court enhance damages; it merely authorizes the court to do so at its discretion. See Modine Mfg. Co. v. Allen Group, Inc., 917 F.2d 538, 543, 16 USPQ2d 1622, 1625 (Fed. Cir. 1990). In exercising this discretion, the trial court considers the weight of the evidence of the infringer's culpability, see Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1581, 24 USPQ2d 1401, 1420 (Fed. Cir. 1992), in light of the factors included in Read. See note 16, *supra* (listing these factors).

CellPro's argument does not take issue with the district court's application of the Read factors. Instead, CellPro returns to its argument that the 1995 jury verdict reflects favorably on its lack of culpability because it illustrates the closeness of the case. See note 16, *supra* (fifth factor). We are once again not convinced that this temporary victory was significantly probative of CellPro's lack of culpability during the early stages of its infringing activity. We believe that the district court adequately justified its decision to treble the damages. See Hopkins II, 978

F. Supp. at 193-96; see also Read, 970 F.2d at 828, 23 USPQ2d at 1436 ("To enable appellate review, a district court is obligated to explain the basis for the [enhanced] reward, particularly when the maximum amount is imposed.").

To summarize, we find no error in either the jury's finding that CellPro willfully infringed the Civin patents or in the decision by the district court to treble damages; we accordingly affirm.

E. The Repatriation Order

CellPro's final argument is that the court exceeded the scope of its power when it ordered the repatriation and destruction of the six vials that it exported to its business partner, Biomira, in Canada, as well as cloned vials and antibodies produced therefrom. CellPro contends that it has not committed an infringing act with respect to the exported vials. CellPro summarizes its activities as follows: it produced approximately 100 vials of 12.8 hybridoma to create a United States master cell bank prior to the issuance of the '204 patent, it exported six of those vials to Canada after issuance, and it used those vials in Canada to supply markets outside of the United States. CellPro asserts that none of these acts -- pre-issuance manufacture, export, or use outside of the United States -- constitutes infringement under 35 U.S.C. Section 271, and accordingly that such acts are beyond the scope of the court's equitable powers.

Hopkins responds that the district court's order was properly predicated on the determination that CellPro used (i.e., by cloning *1723 or testing) other vials from its United States cell bank in the United States after the issuance of the patent and thereby infringed with respect to the United States cell bank "as a whole." Hopkins asserts that the injunctive power of the district courts is not limited to the prohibition of those activities that constitute patent infringement, but also extends to prohibitions necessary in order to fashion a meaningful remedy for past infringement. Hopkins argues that repatriation in this case is such a meaningful remedy and will prevent CellPro from unfairly capitalizing upon its infringement.

Section 283 of the Patent Code empowers the courts to "grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable." 35 U.S.C. Section 283 (1994). In accordance with the clear wording of this section, "an injunction is only proper to the extent it is 'to prevent the violation of any right secured by patent.' "Eli

Lilly & Co. v. Medtronic, Inc., 915 F.2d 670, 674, 16 USPQ2d 2020, 2024 (Fed. Cir. 1990) (quoting 35 U.S.C. Section 283). A "necessary predicate" for the issuance of a permanent injunction is therefore a determination of infringement. *Id.* When deciding whether a district court abused the discretion provided by Section 283, we are mindful of the fact that the district courts are in the best position to fashion an injunction. See Joy Techs., Inc. v. Flakt, Inc., 6 F.3d 770, 777, 28 USPQ2d 1378, 1384 (Fed. Cir. 1993) (citation omitted). However, judicial restraint of lawful noninfringing activities must be avoided. See *id.* (citing Deepsouth Packing Co. v. Laitram Corp., 406 U.S. 518, 529-31, 173 USPQ 769, 773-74 (1972)).

[8] We agree with CellPro that the district court abused its discretion in ordering the repatriation and destruction of the exported vials. The repatriation aspect of the order does not enjoin activities that either have infringed the '204 patent or are likely to do so and thus does not prevent infringement -- the proper purpose of an injunction under Section 283. It is clear that the six vials standing alone have not infringed the '204 patent. Mere possession of a product which becomes covered by a subsequently issued patent does not constitute an infringement of that patent until the product is used, sold, or offered for sale in the United States during the term of the patent. See Cohen v. United States, 487 F.2d 525, 527, 179 USPQ 859, 860 (Ct. Cl. 1973); Columbia & N.R.R. Co. v. Chandler, 241 F. 261 (9th Cir. 1917) (holding that, while the patentee could not recover damages for the manufacture of infringing trucks prior to the issuance of the patent, it did not follow "that the trucks were set free from the monopoly of the patent, and could thereafter be used, without liability to the inventor"); see also Hoover Group, Inc. v. Custom Metalcraft, Inc., 66 F.3d 299, 304, 36 USPQ2d 1101, 1104 (Fed. Cir. 1995) ("[The patentee] may of course obtain damages only for acts of infringement after the issuance of the patent."). Likewise, neither export from the United States nor use in a foreign country of a product covered by a United States patent constitutes infringement. See 35 U.S.C. Section 271(a) (1994) ("[W]hoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent."); see also Paper Converting Mach. Co. v. Magna- Graphics Corp., 745 F.2d 11, 16, 223 USPQ 591, 594 (Fed. Cir. 1984) ("[B]y the terms of the patent grant, no

activity other than the unauthorized making, using, or selling of the claimed invention can constitute direct infringement of a patent, no matter how great the adverse impact of that activity on the economic value of a patent.") (emphasis in original).

That CellPro used other vials from the cell bank in an infringing manner in the United States does not taint the six exported vials with infringement. [FN31] The exported vials were not "guilty by association." One may consider the pre-issuance manufacture of two machines, one of which is used after the patent is issued and the other of which is exported. An injunction requiring return of the exported machine, which was never made, used, or sold during the term of the patent in the United States, is beyond the scope of Section 283 and hence an abuse of discretion. The same principle applies here to the vials exported to Canada. Accordingly, the court's conclusion that use of some of the vials of the cell bank constituted a use of the cell bank *1724 "as a whole" as a means of justifying its repatriation order was an abuse of discretion.

Moreover, there is also no evidentiary basis for concluding that the district court's order was necessary to prevent CellPro from committing further infringing activities. An injunction under Section 283 can reach extraterritorial activities such as those at issue here, even if these activities do not themselves constitute infringement. It is necessary however that the injunction prevent infringement of a United States patent. For example, in Spindelfabrik Suessen-Schurr v. Schubert & Salzer, 903 F.2d 1568, 14 USPQ2d 1913 (Fed. Cir. 1990), the infringer argued that the district court's injunction "impermissibly extend [ed] the reach of American patent law beyond the boundaries of the United States" because it prohibited the infringer from making, in Germany, machines "for use in the United States" and machines "destined for delivery to the United States." This court held that the injunction was "a reasonable and permissible endeavor to prevent infringement in the United States and not a prohibited extra-territorial application of American patent law. They were well within the district court's authority." *Id.* at 1578, 14 USPQ2d at 1921 (emphasis added).

The record in this case does not, as in Spindelfabrik, suggest that the exported vials will be used in a manner which will infringe the patent. CellPro has stipulated, and Hopkins does not refute, that Biomira intended to produce antibodies for CellPro in Canada "for use in products to be sold outside of the United States." CellPro's Opening Brief at 40 (citing the

declaration of John P. Bordonaro, at Joint App. A513, A515-16 ("At no time has CellPro imported back into the United States the 12.8 monoclonal antibodies manufactured by Biomira in Canada or the cell suspension derived from using the 12.8 monoclonal antibodies.")). Because the record is devoid of evidence upon which the district court could have concluded that its order would prevent further infringement, there was no basis for the court to order the exported hybridomas and its byproducts to be shipped to the United States.

We also do not find persuasive Hopkins' argument that the scope of the district court's order can be justified because it is necessary to fashion a meaningful remedy for CellPro's past infringement. Section 283 does not provide remedies for past infringement; it only provides for injunctive relief to prevent future infringement. The section under which a litigant must seek compensation for past infringement is Section 284. See 35 U.S.C. Section 284, Para. 1 (1994) ("Upon finding for the claimant the court shall award the claimant damages adequate to compensate for the infringement."). We do not understand Hopkins to seriously dispute that it has not received adequate compensation for CellPro's infringement. However, to the extent that Hopkins complains that CellPro's infringement has damaged its ability to service foreign markets, Hopkins must rely on foreign patent protection. See Deepsouth, 406 U.S. at 531, 173 USPQ at 774 ("Our patent system makes no claim to extraterritorial effect. . . . To the degree that the inventor needs protection in markets other than those of this country, the wording of 35 U.S.C. Sections 154 and 271 reveals a congressional intent to have him seek it abroad through patents secured in countries where his goods are being used.") (citations and quotation omitted). Such a complaint cannot be remedied by the imposition of an injunction under Section 283.

Hopkins further argues, mimicking the district court's "as a whole" rationale, that it would be fair under the circumstances to order repatriation and destruction because CellPro has committed other clear acts of infringement with respect to other vials in the United States cell bank. We do not agree. As we have already stated, we disagree that this rationale provides a sufficient premise for the court's order given the facts of this case. Moreover, premising the order on this rationale amounts to punishment of CellPro for its infringement. This is not the proper purpose of injunctive relief under Section 283. See Amstar Corp. v. Envirotech Corp., 823 F.2d 1538, 1549, 3 USPQ2d 1412, 1420 (Fed. Cir. 1987) (noting

that " [p]unishment is not the purpose of an injunction" under Section 283 and citing Hecht Co. v. Bowles, 321 U.S. 321, 329 (1944), for the proposition that the "historic injunctive process was designed to deter, not to punish").

Those portions of the district court's permanent injunction order that ordered repatriation and destruction of vials exported by CellPro to Biomira and by-products produced thereby are not consistent with the stated purpose of Section 283 -- to prevent infringement. Thus, the court abused its discretion, and those portions of the order are vacated.

Both sides have raised further arguments in support of their various positions. We have considered all such arguments, but they do not alter our conclusions.

CONCLUSION

The court erred in concluding that CellPro waived its right to rely on the Morstyn reference *1725 in establishing that the claims of the '680 patent are invalid under 35 U.S.C. Section 103 (1994). We accordingly vacate the court's grant of summary judgment in favor of Hopkins and remand for further proceedings on this issue. The court also abused its discretion in ordering the repatriation and destruction of vials of hybridoma which CellPro exported to Biomira in Canada and by-products thereof. We accordingly vacate these portions of the court's permanent injunction order. The court did not err in any other respect. The decision of the court is therefore

AFFIRMED-IN-PART, VACATED- IN-PART and
REMANDED.

FN1 The written description portions of both patents' specifications are identical.

FN2 The specification states that mature T-cells are a cause of GVHD in animals. See, e.g., '680 patent, col. 1, ll. 36-37.

FN3 "Monoclonal antibodies" are defined as "[a] population of identical antibodies. . . , all of which recognize the same specific [epitope] on a simple or complex antigen."

Paul Singleton & Diana Sainsbury, Dictionary of Microbiology and Molecular Biology 431 (2d ed. 1993); see also Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1369-70, 231 USPQ 81, 82 (Fed. Cir. 1986); In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

FN4 Fluorescence-activated coating separation ("FACS") "involves coating the antibody with a colored dye. All the cells in the coated sample then are passed through a machine that uses a laser to identify and separate the cells based on their color." Hopkins I, 931 F. Supp. at 309.

FN5 A "hybridoma" is defined as " [t]he product and/or progeny of cell fusion . . . between a [tumor] cell and a non- [tumor] cell; the in vitro production of hybridomas is carried out to provide continuously replicating (hybrid) cells which exhibit some or all of the characteristics of the non- [tumor] cell . . . ; such hybridomas are used, e.g., as sources of monoclonal antibodies." Singleton & Sainsbury, *supra* note 3, at 562.

FN6 Because the My-10 antigen disappears as a cell matures, but is present on all forms of stem cells, it is said to be "stage-specific," not lineage dependent. See '680 patent, col. 4, ll. 43-48.

FN7 Claim 1 of the '204 patent contains several other limitations which describe, for example, the specific cells on which the antigen is present. As the parties have not brought these limitations to our attention, we presume that the parties do not dispute that CellPro's antibody meets these limitations.

FN8 As stated by the trial court, "CellPro's process for purifying stem cells works as follows. CellPro adds blood cells to some of the 12.8 antibody that has been previously bound to biotin. These cells are poured into a column, inside of which are beads covered with avidin. Avidin binds tightly with biotin, locking the [stem] cells onto the walls of the column while the other [mature] cells are

washed away. The column is then agitated to loosen the [stem] cells to obtain a purified suspension of stem cells." Hopkins I, 931 F. Supp. at 312.

FN9 Apparently because neither CellPro's Ceprate machines nor its production of 12.8 antibody directly infringed the "cell suspension" claims of the '680 patent, Hopkins sued CellPro for inducing infringement and contributory infringement. See Hopkins I, 931 F. Supp. at 307.

FN10 Table 9 indicates that "3% of the FACS-Separated My-10-antigen- positive cells were matured neutrophils . . . , 6% were mature monocytes, and 1% were mature lymphocytes." '680 patent, col. 18, tbl. 9 n.*. Thus, there are $3\% + 1\% + 6\% = 10\%$ mature cells in the disclosed cell suspension.

"Neutrophils," "monocytes," and "lymphocytes" are defined as types of "leucocytes," which in turn are defined as "the white cells of the blood and lymphoid system." Singleton & Sainsbury, *supra* note 3, at 498.

FN11 Specifically, CellPro proffered two expert declarations, one from Dr. H. Mark Jones concluding that Morstyn anticipated the claims, and one from Dr. C. Glenn Begley concluding that the claims were either "anticipated and/or obvious in view of [Beverly] and/or [Morstyn]."

FN12 Although the court expressly rejected only Jones's testimony, we interpret the court's reasoning to have precluded any argument that relied on Morstyn, including the argument that Beverly in combination with Morstyn would have rendered the asserted claims obvious.

On May 6, 1998, CellPro informed this court that, in response to the district court's invitation, CellPro subsequently briefed the district court on the issue of admissibility of Jones's testimony. After Hopkins had the opportunity to respond, the district court declined to reconsider its prior decision on this issue. See

Johns Hopkins Univ. v. CellPro, Civ. No. 94-105-
RRM (D. Del. Jan. 17, 1997) (transcript).

FN13 "CD" stands for "cluster designation," which is used by those skilled in the art to group together antibodies that exhibit similar binding characteristics, particularly binding to the same antigen. As explained by CellPro in its brief to this court: "[i]n an attempt to classify and to organize the large numbers of new blood cell antibodies that are generated in laboratories each year, panels of scientists review research data and designate clusters of antibodies that appear to have similar binding characteristics. CD34 is the 34th cluster so designated." CellPro's Opening Brief at 5 n.2. Thus, although "CD34" technically refers to a genus of antibodies that bind to a particular entity, scientists generally refer to that entity as "the CD34 antigen." Both parties generally agree that the anti-My-10 and 12.8 antibodies have been properly classified as CD34 antibodies.

FN14 The Kohler/Milstein method involves first immunizing a mouse with a human cell [the immunogen], which makes the mouse capable of producing the relevant antibody. The mouse's B cells, the ones that produce antibodies, are then removed and chemically fused with an immortal cancer cell line from a mouse. The fused cells, called hybridomas, will have the combined qualities of a B cell and the cancer cell line--they will be immortal and they will have the ability to make one antibody. The hybridomas are then screened to discover an antibody that has the characteristic being sought, in this case one that binds to an antigen on stem cells but not on mature cells.

Hopkins I, 931 F. Supp. at 309. Civin used a human immortal cancer cell line, known as KG-1a, as the immunogen in this process. Civin knew that these cells had characteristics similar to immature cells and therefore that they might have similar antigens on their surfaces and might stimulate the production of antibodies capable of binding to antigens on immature stem cells. See *id.*

FN15 35 U.S.C. Section 284, Para. 2 (1994) provides in relevant part that "the court may increase the damages up to three times the amount found or assessed" in a patent infringement action.

FN16 These factors include: (1) whether the infringer deliberately copied the ideas or design of another, (2) whether the infringer, when he knew of the other's patent protection, investigated the scope of the patent and formed a good-faith belief that it was invalid or that it was not infringed, (3) the infringer's behavior as a party to the litigation, (4) the infringer's size and financial condition, (5) the closeness of the case, (6) the duration of the infringer's misconduct, (7) any remedial action by the infringer, (8) the infringer's motivation for harm, and (9) whether the infringer attempted to conceal its misconduct. See Read, 970 F.2d at 827, 23 USPQ2d at 1435-36.

FN17 CellPro also notes that the applicant referred to this purported definition of the words "substantially free" during the reexamination of the '680 patent, at which time the applicant was attempting to distinguish its claims over the Beverley reference. Because the relevant excerpts from the reexamination prosecution history are largely redundant with the prosecution history summarized above, we do not reiterate them here.

FN18 Hopkins intimates in its brief that the specification discloses other cell suspensions of lesser purities, but it has not specifically identified them and we do not find them in the specification.

FN19 Equally unremarkable is the confirmation of the patentability of the claims during reexamination over the Beverley reference, which the applicant and the examiner agreed were "significantly contaminated with small lymphocytes," including T-cells.

FN20 "After [a pretrial] conference held pursuant to this rule, an order shall be entered reciting the action taken. This order shall control the subsequent course of the action unless modified by a subsequent order. The order following a final pretrial conference shall be modified only to prevent manifest injustice." Fed. R. Civ. P. 16(e).

FN21 We note that although the court granted a new trial on the issue of obviousness, it was not improper for CellPro to subsequently present an argument that the claims were anticipated: " [A] disclosure that anticipates under Section 102 also renders the claim invalid under Section 103, for 'anticipation is the epitome of obviousness.' Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 1548, 220 USPQ 193, 198 (Fed. Cir. 1983) (citing In re Fracalossi, 681 F.2d 792, 215 USPQ 569 (CCPA 1982)).

FN22 We express no opinion as to whether summary judgment may or may not be appropriate upon remand.

FN23 Hopkins also points out that the examiner subsequently placed her imprimatur on the idea that My-10 and "the CD34 antigen" were synonymous, noting that the claims were limited to those monoclonal antibodies reactive with "a particular antigen (now identified as CD34)." See Joint App. at EA7954.

FN24 An "epitope" is defined as "any region of the [antigen] macromolecule with the ability or potential to elicit, and combine with, specific antibody." Singleton & Sainsbury, *supra* note 3, at 269, 323.

FN25 The Kg-1a cell line is a variant of the Kg-1 cell line. See '204 patent, col. 3, ll. 44-47. Both of these cell lines and samples of the hybridoma produced thereby are readily available to the public, and the '204 patent discloses the locations at which both of these starting materials may be procured. Such public deposits of living materials may

enable a claimed invention whose manufacture or use depends thereupon, see, e.g., Wands, 858 F.2d at 735 & n.8, 8 USPQ2d at 1403 & n.8, but Hopkins does not attempt to refute CellPro's enablement challenge by relying on these deposits. In any event, because we conclude that CellPro's challenge fails even without consideration of the deposits, we need not comment on their relevance.

FN26 The district court noted that "[t]estimony at trial established that a person skilled in the art of making monoclonal antibodies must have a bachelor's degree in the appropriate scientific field and must have made a monoclonal antibody at least once." Hopkins I, 931 F. Supp. at 323. CellPro does not contest this definition of one of ordinary skill in this art.

FN27 Dr. C.E. Van der Schoot's expert declaration filed in opposition to Hopkins' summary judgment motion is inapposite for the same reason. Van der Schoot concluded "that there were numerous differences between [the] immunization protocol [which we] used to obtain three monoclonal CD34 antibodies . . . and Dr. Civin's immunization protocol disclosed in the '204 patent." Joint App. at A23420. The deposition testimony of Dr. Gustav Gaudernack, also relied on by CellPro, evidences a similar failing to follow the disclosure of the '204 patent. Gaudernack testified that he followed neither the disclosed immunization protocol nor the disclosed screening protocol. See id. at A22612.

FN28 Wijdenes opined that the KG-1 and KG-1a cell lines are equivalent immunogens for purposes of producing CD34 antibodies. See Joint App. at A23343.

FN29 Finally, we note that Wijdenes, like Van der Schoot and Gaudernack, see note 27, *supra*, "did not copy the protocol described in [the '204 patent] specification," Joint App. at A23361. This provides yet another reason for concluding that Wijdenes's testimony did not bear

significantly on enablement.

FN30 In *Datascope*, the district court helped to justify its conclusion that the infringer did not act willfully by noting that this court had earlier split 2-1 in affirming the judgment that the infringer was liable. The district court felt that this court's non-unanimity buttressed "an honest doubt . . . as to the validity and infringement of *Datascope's* patents" as reflected in legal opinions which the infringer procured during the development of its infringing device. *Datascope*, 879 F.2d at 823, 11 USPQ2d at 1323. We reversed the finding of nonwillfulness, stating:

The district court's reference to this court's 2-1 decision affirming the judgment of liability was inappropriate in this case. That decision was rendered several years after the date infringement began (i.e., the date employed in determining willfulness under the circumstances of this case), and was based on facts unrelated to [the infringer's] decision on the critical date.

Id. at 828, 11 USPQ2d at 1327 (citations omitted).

FN31 We do not suggest, and neither party argues, that the court had no injunctive power with respect to those vials which were not exported but which were also not used in the United States. That these vials, like the exported vials, did not infringe does not free them from the court's equitable power under Section 283. Because CellPro had used some of its vials in the United States, a clear act of infringement, its propensity to infringe has been sufficiently established such that the court could conclude that enjoining the use of United States-based vials was necessary to prevent infringement.

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47 U.S.P.Q.2d 1705

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Transfer of Genes to Humans: Early Lessons and Obstacles to Success

Ronald G. Crystal

Enough information has been gained from clinical trials to allow the conclusion that human gene transfer is feasible, can evoke biologic responses that are relevant to human disease, and can provide important insights into human biology. Adverse events have been uncommon and have been related to the gene delivery strategies, not to the genetic material being transferred. Human gene transfer still faces significant hurdles before it becomes an established therapeutic strategy. However, its accomplishments to date are impressive, and the logic of the potential usefulness of this clinical paradigm continues to be compelling.

Human gene transfer is a clinical strategy in which the genetic repertoire of somatic cells is modified for therapeutic purposes or to help gain understanding of human biology (1, 2). Essentially, gene transfer involves the delivery, to target cells, of an expression cassette made up of one or more genes and the sequences controlling their expression. This can be carried out *ex vivo* in a procedure in which the cassette is transferred to cells in the laboratory and the modified cells are then administered to the recipient. Alternatively, human gene transfer can be done *in vivo*, in a procedure in which the expression cassette is transferred directly to cells within an individual. In both strategies, the transfer process is usually aided by a vector that helps deliver the cassette to the intracellular site where it can function appropriately (1, 2).

Once considered a fantasy that would not become reality for generations, human gene transfer moved from feasibility and safety studies in animals to clinical applications more rapidly than expected by even its most ardent supporters (1-3). It is not the purpose of this review to detail all human protocols that have been proposed, but to use examples from the available information regarding ongoing human trials (3) to define the current status of the field.

How Is Human Gene Transfer Carried Out?

The choice of an *ex vivo* or *in vivo* strategy and of the vector used to carry the expression cassette is dictated by the clinical target. The vector systems for which data are available from clinical trials (retroviruses, adenoviruses, and plasmid-liposome com-

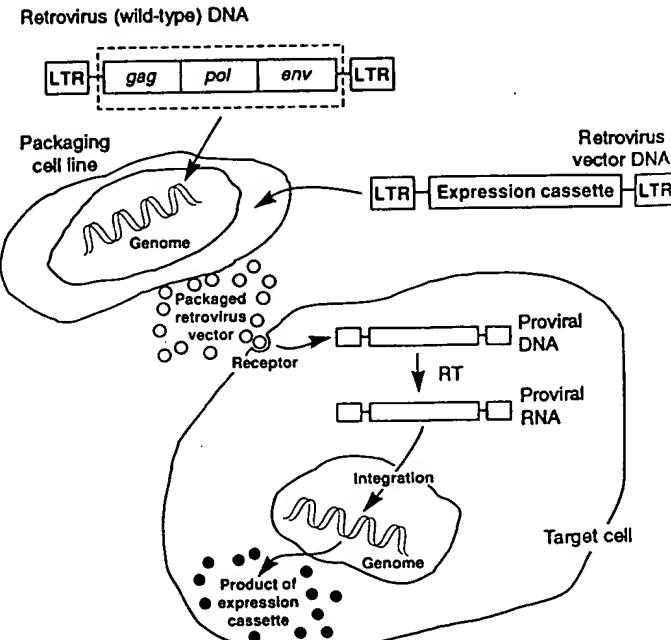
plexes) transfer expression cassettes through different mechanisms and thus have distinct advantages and disadvantages for different applications (1, 2).

Vectors. Replication-deficient, recombinant retrovirus vectors can accommodate up to 9 kb of exogenous information (Fig. 1). Retroviruses transfer their genetic information into the genome of the target cell, and thus, theoretically, the target cell's genotype is permanently modified (1, 2, 5). This is an advantage when treating hereditary and chronic disorders, but it has risks, including the potential for toxicity associated with chronic overexpression or insertional mutagenesis (for example, if the pro-

viral DNA randomly disrupts a tumor suppressor gene or activates an oncogene). The use of retrovirus vectors is limited by the sensitivity of the vector to inactivation, by the fact that target cells must proliferate in order to integrate the proviral DNA into the genome, and by production problems associated with recombination, rearrangements, and low titers (1, 2, 5). Retrovirus vectors have been used almost entirely in *ex vivo* gene transfer trials.

Adenovirus vectors in current use accommodate expression cassettes up to 7.5 kb (1, 2, 6). These vectors enter the cell by means of two receptors: a specific receptor for the adenovirus fiber and $\alpha_1\beta_3$ (or $\alpha_1\beta_5$) surface integrins that serve as a receptor for the adenovirus penton (7) (Fig. 2). Adenovirus vectors are well suited for *in vivo* transfer applications because they can be produced in high titers (up to 10^{13} viral particles/ml) and they efficiently transfer genes to nonreplicating and replicating cells (8). The transferred genetic information remains epichromosomal, thus avoiding the risks of permanently altering the cellular genotype or of insertional mutagenesis. However, adenovirus vectors in current use evoke nonspecific inflammation and antivector cellular immunity (9). These responses, together with the epichromosomal position of the expression cassette, limit the duration of expression to periods ranging from weeks to months. Thus adenovirus vectors will have to be readministered periodically to maintain their persistent expression. Although it is unlikely that

Fig. 1. Retrovirus vector design, production, and gene transfer. Retroviruses are RNA viruses that replicate through a DNA intermediate. The retrovirus vectors administered to humans all use the Maloney murine leukemia virus as the base. The *gag*, *pol*, and *env* sequences are deleted from the virus, rendering it replication-deficient. The expression cassette is inserted, and the infectious replication-deficient retrovirus is produced in a packaging cell line that contains the *gag*, *pol*, and *env* sequences that provide the proteins necessary to package the virus. The vector with its expression cassette enters the target cell via a specific receptor. In the cytoplasm, the reverse transcriptase (RT) carried by the vector converts the vector RNA into the proviral DNA that is randomly integrated into the target cell genome, where the expression cassette makes its product.



The author is professor of medicine and chief of the Division of Pulmonary and Critical Care Medicine, The New York Hospital-Cornell Medical Center, 520 East 70th Street, ST505, New York, NY 10021, USA.

repeat administration will be risky, it is not known whether antibodies directed against vector capsid proteins will limit the efficacy of repetitive administration of these vectors (9). Adenovirus vectors have been used only in *in vivo* human trials.

In theory, plasmid-liposome complexes have many advantages as gene transfer vectors, in that they can be used to transfer expression cassettes of essentially unlimited size, cannot replicate or recombine to form an infectious agent, and may evoke fewer inflammatory or immune responses because they lack proteins (10) (Fig. 3). The disadvantage of these vectors is that they are inefficient, requiring that thousands of plasmids be presented to the target cell in order to achieve successful gene transfer. The available data are not sufficient to determine if repetitive administration of liposomes or

DNA poses safety risks. Plasmid-liposome complexes have been used only in *in vivo* human trials.

Expression cassettes and clinical targets. Human gene transfer studies fall into two categories: marking and therapeutic (Table 1). The marking studies use expression cassettes with bacterial antibiotic-resistant genes, which allow the genetically modified cells to be identified (Table 1). Because the marking genes have no function (other than to permit selection of the modified cells *in vitro*), the trials using marker genes have been designed to demonstrate the feasibility of human gene transfer, to uncover biologic principles relevant to human disease, and to evaluate safety. These trials have mostly used retrovirus vectors and have focused on malignant disorders or on human immunodeficiency virus (HIV) infection.

Fig. 2. Adenovirus vector design, production, and gene transfer. Adenoviruses are DNA viruses with a 36-kb genome. The wild-type adenovirus genome is divided into early (E1 to E4) and late (L1 to L5) genes. All adenovirus vectors administered to humans use adenovirus serotypes 2 or 5 as the base. The ability of the adenovirus genome to direct production of adenoviruses is dependent on sequences in E1. To produce an adenovirus vector, the E1 sequences (and E3 sequences if the space is needed) are deleted. The expression cassette is inserted, and the vector DNA is transfected into a complementing cell line with E1 sequences in its genome. The adenovirus vector with its expression cassette is E1- and thus incapable of replicating. The vector binds to the target cell through an interaction of the adenovirus fiber and penton, each to a specific receptor; moves into a cytoplasmic endosome; and breaks out and delivers its linear, double-stranded DNA genome with the expression cassette into the nucleus, where it functions in an epichromosomal fashion to direct the expression of its product.

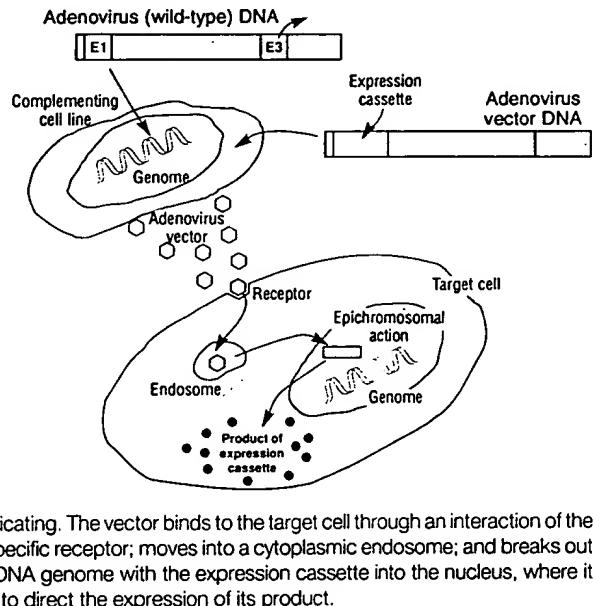
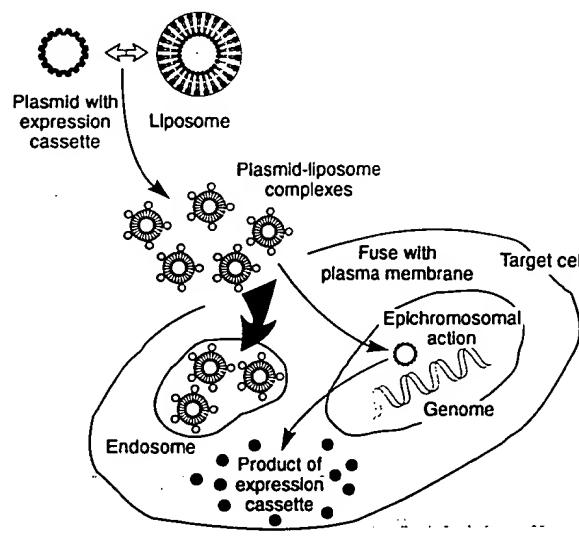


Fig. 3. Plasmid-liposome complex design and gene transfer. The liposomes used in human gene transfer trials have various compositions, but typically include synthetic cationic lipids. The positively charged liposome is complexed to the negatively charged plasmid with its expression cassette. The complexes enter the target cell by fusing with the plasma membrane. The vector does not have an inherent macromolecular structure that conveys information to enable efficient translocation of the plasmid to the nucleus. Consequently, most of the newly introduced genetic material is wasted as it is shunted to cytoplasmic organelles. When used *in vivo*, it is likely that most, if not all, of the plasmids that reach the nucleus function in an epichromosomal fashion.



The therapeutic trials seek to transfer expression cassettes carrying genes that will evoke biologic responses that are relevant to the treatment of human disease, and to demonstrate that this can be accomplished safely. The therapeutic studies have used retrovirus vectors, adenovirus vectors, or plasmid-liposome complexes. All of the therapeutic trials have been directed toward monogenic hereditary disorders or cancer.

What Has Really Been Accomplished?

Feasibility of gene transfer. Probably the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible. Although gene transfer has not been demonstrated in all recipients, most studies have shown that genes can be transferred to humans whether the strategy is *ex vivo* or *in vivo*, and that all vector types function as intended. Taken together, the evidence is overwhelming, with successful human gene transfer having been demonstrated in 28 *ex vivo* and 10 *in vivo* studies (Table 1).

In the *ex vivo* studies with retrovirus vectors, successful gene transfer to humans has been shown by the transfer of marker genes to various classes of T cells (11–16), to stem cells in blood and marrow (16–27), to tumor-infiltrating lymphocytes (TILs) (11, 28, 29), to neoplastic cells of hematopoietic lineage (16, 17, 20, 21, 25, 26), and to neoplastic cells derived from solid tumors (Table 1). Although there is variation among *ex vivo* clinical trials in the proportion of genetically marked cells recovered from the recipients, retroviral vector DNA or marker gene-derived mRNA or both have been observed in cells collected after periods ranging from several weeks to 36 months after administration.

Retrovirus vectors also have been used to transfer therapeutic genes *ex vivo*, with success demonstrated by the fact that the modified cells exhibit their altered phenotype *in vivo* for up to 36 months (Table 1). Typically, the expression cassette containing the therapeutic gene also contains an antibiotic-resistance gene, permitting the *ex vivo* selection of genetically modified cells recovered from the recipient. Successful gene transfer has been demonstrated in cells recovered from children with adenosine deaminase (ADA) deficiency after transfer of the normal ADA complementary DNA (cDNA) to autologous T cells, cord blood, and placental cells (30–32); from individuals with solid tumors after transfer of cytokine cDNAs in autologous vaccine strategies to fibroblasts, TILs, or tumor cells (33–37); from individuals with familial hypercholesterolemia after transfer of the low-density lipoprotein (LDL) receptor cDNA to autologous hepatocytes (38, 39);

from HIV⁺ siblings after transfer of a chimeric T cell receptor cDNA to blood T cells of a twin (40); and from individuals with tumors who received autologous marrow transplants after transfer of the multidrug resistance 1 cDNA to autologous blood CD34⁺ stem cells (41). A retrovirus vector has also been used in vivo to successfully transfer a p53 antisense cDNA to lung carcinoma cells (42). Finally, in a combined ex vivo-in vivo strategy for treatment of brain neoplasms, gene transfer to tumor cells has been observed after xenografting.

neic cells (murine fibroblasts whose genome had been modified with amphotropic packaging sequences) infected with a retrovirus vector containing an expression cassette with the herpes simplex thymidine kinase (HSTK) gene were introduced into the tumor (43).

In in vivo studies with adenovirus vectors, several studies have shown that direct administration of a vector containing the normal human cystic fibrosis transmembrane conductance regulator (CFTR) cDNA to the nasal or bronchial epitheli-

um of individuals with cystic fibrosis (CF) results in transfer of the CFTR cDNA-containing expression cassette to the epithelium, where CFTR mRNA or protein is expressed for at least 9 days (44-50) (Table 1). Direct administration of a plasmid-liposome complex containing an expression cassette with the CFTR cDNA to the nasal epithelium of individuals with CF resulted in expression of CFTR mRNA in the epithelium (51). Finally, plasmid-liposome complexes have

Table 1. Summary of studies showing that transfer of genes to humans is feasible. Data shown are based on published articles and abstracts and on RAC-mandated biannual reports of principal investigators as of the RAC meeting of 8 to 9 June 1995. Abbreviations used for vector study type are RV, retrovirus; Ad, adenovirus; PL, plasmid-liposome complex; M, marker-type study; and T, therapeutic-type study. Abbreviations used for gene products are Neo^R, neomycin phosphotransferase; Hygro, hygromycin phosphotransferase; HSTK, herpes simplex thymidine kinase; ADA, adenosine deaminase; LDLR, low-density lipoprotein receptor; TNF, tumor necrosis factor α ; CD4 zeta-R, chimeric T cell receptor; MDR-1, multidrug resistance 1; IL-4, interleukin 4; GM-CSF, granulocyte macrophage colony-stimulating factor; CFTR, cystic fibrosis transmembrane conductance regulator; and B7 + β_2 , histo-

compatibility locus antigen class I-B7 + β_2 microglobulin. Except for Neo^R, Hygro, and HSTK, all genes are cDNAs. Abbreviations used for target cells are TIL, tumor-infiltrating lymphocytes; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus 1; and CTL, cytotoxic T lymphocytes. All target cells are autologous unless otherwise specified. Abbreviations used to characterize study populations are AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; ALL, acute lymphocytic leukemia; ca, carcinoma; and CF, cystic fibrosis. Under in vivo evidence of gene transfer, a plus sign indicates a report of transfer or expression (or both) of an exogenous gene in cells obtained from one or more individuals in the study; time listed is the longest time after administration that gene transfer or expression was observed.

Vector study type	Gene product	Target cells	Study population	In vivo evidence of gene transfer	Principal investigator	Reference number
RV-M	Neo ^R	TIL	Melanoma	+ 2 months	Rosenberg, S. A.	(28)
RV-M	Neo ^R	TIL	Melanoma	+ 3 months	Lotze, M. T.	(29)
RV-M	Neo ^R	Marrow	AML	+36 months	Brenner, M. K.	(16, 17)
RV-M	Neo ^R	Marrow	Neuroblastoma	+29 months	Brenner, M. K.	(18)
RV-M	Neo ^R	Marrow	Neuroblastoma	+20 months	Brenner, M. K.	(18)
RV-M	Neo ^R	Marrow	CML	+ 5 months	Deisseroth, A. B.	(20)
RV-M	Neo ^R	Marrow	AML, ALL	+12 months	Cornetta, K.	(21)
RV-M	Neo ^R	CD4 ⁺ , CD8 ⁺ , blood, TIL	Melanoma, renal cell ca	+	Economou, J. S.	(11)
RV-M	Neo ^R	CD34 ⁺ blood, marrow	Multiple myeloma	+18 months	Dunbar, C. E.	(22, 23)
RV-M	Neo ^R	CD34 ⁺ blood, marrow	Breast ca	+18 months	Dunbar, C. E.	(23, 24)
RV-M	Neo ^R	Marrow	AML	+12 months	Brenner, M. K.	(25)
RV-M	Neo ^R	Normal twin blood T cell [†]	Identical twins, 1 HIV ⁺	+ 4 months	Walker, R. E.	(12)
RV-M	Neo ^R	Blood, marrow	CML	+	Deisseroth, A. B.	(26)
RV-M	Neo ^R	CD34 ⁺ blood	Metastatic ca, lymphoma	+15 days	Schuening, F. G.	(27)
RV-M	Neo ^R	EBV-specific CTL [‡]	Ca, leukemia	+ 7 months	Heslop, H. E.	(14, 15)
RV-M	Hygro + HSTK	CD8 ⁺ HIV gag specific, CTL [§]	HIV ⁺ , lymphoma	+14 days	Greenberg, P.	(13)
RV-T	ADA	Blood T cells	ADA deficiency	+36 months	Blaese, R. M.	(30, 31)
RV-T	ADA	Cord blood cells	ADA deficiency	+18 months	Blaese, R. M.	(30, 32)
RV-T	LDLR	Hepatocytes	Familial hypercholesterolemia	+ 4 months	Wilson, J. M.	(38, 39)
RV-T	TNF	TIL	Melanoma	+	Rosenberg, S. A.	(33)
RV-T	IL-2	Tumor cells	Metastatic ca	+	Rosenberg, S. A.	(36)
RV-T	IL-2	Neuroblastoma	Metastatic ca	+	Brenner, M. K.	(35)
RV-T	CD4 zeta-R	Normal twin blood T cell [†]	Identical twins, 1 HIV ⁺	+ 4 months	Walker, R. E.	(40)
RV-T	MDR-1	Blood CD34 ⁺	Breast ca	+	Deisseroth, A. B.	(41)
RV-T	IL-4	Fibroblasts [¶]	Metastatic ca	+	Lotze, M. T.	(34)
RV-T	GM-CSF	Melanoma	Melanoma	+	Dranoff, G.	(37)
RV-T	Anti-sense p53	Lung ca	Lung ca	+ 1 days	Roth, J. A.	(42)
RV-T*	HSTK	Tumor cells	Glioblastoma	+	Oldfield, E. H.	(43)
Ad-T	CFTR	Nasal, airway epithelium	CF	+ 9 days ⁼	Crystal, R. G.	(44, 45)
Ad-T	CFTR	Nasal epithelium	CF	+	Welsh, M. J.	(46, 47)
Ad-T	CFTR	Nasal epithelium	CF	+	Welsh, M. J.	(48)
Ad-T	CFTR	Airway epithelium	CF	+ 5 days ^{**}	Wilson, J. M.	(49)
Ad-T	CFTR	Nasal epithelium	CF	+	Boucher, R. C.	(50)
PL-T	CFTR	Nasal epithelium	CF	+ 4 days	Geddes, D. M.	(51)
PL-T	B7 + β_2	Melanoma	Metastatic ca	+ 3 days	Nabel, G. J.	(52)
PL-T	B7 + β_2	Colorectal ca	Metastatic ca	+	Rubin, J. T. ^{††}	(53, 54)
PL-T	B7 + β_2	Renal cell ca	Metastatic ca	+	Volgelzang, N. ^{††}	(54, 55)
PL-T	B7 + β_2	Melanoma	Metastatic ca	+	Hersh, E. ^{††}	(56)

*This study used a mixed ex vivo-in vivo strategy, in which a xenogenic fibroblast cell line was modified with a retrovirus to produce an amphotropic retrovirus vector containing an expression cassette with the genes for Neo^R + HSTK, and the modified retrovirus-producing cell line was administered directly into the tumor. [†]Blood T cells from a normal identical twin modified with an expression cassette and then administered to an HIV⁺ twin. [‡]Allogeneic. [§]The HSTK gene used as a marker gene. ^{||}Autologous tumor cells modified with an expression cassette, lethally irradiated, and then administered as a "vaccine." [¶]Autologous fibroblasts modified with an expression cassette, lethally irradiated, and then administered together with autologous, unmodified tumor cells as a "vaccine." ⁼Messenger RNA at 9 days, vector DNA at 15 days. ^{**}A few + cells were observed at 90 days. ^{††}Collaborative study, different institutions.

been used to transfer the human leukocyte antigen (HLA)-B7 and β_2 microglobulin cDNAs directly to solid tumors *in vivo*, with consequent expression of the transfer cassette being seen in the tumor (52-56).

Relevant biologic responses. No human disease has been cured by human gene transfer, and it is not clear when this will be accomplished. However, several studies have demonstrated that therapeutic genes transferred to humans by means of retrovirus, adenovirus, and plasmid-liposome vectors can evoke biologic responses that are relevant to the gene product and to the specific disease state of the recipient (Table 2). Most of the studies demonstrating biologic efficacy have focused on monogenic hereditary disorders, where it is rational to believe that, if the normal gene product could be appropriately expressed at the relevant site, the abnormal biologic phenotype could be corrected.

Severe combined immunodeficiency-ADA deficiency is a fatal recessive disorder caused by mutations in the gene encoding ADA; these mutations cause accumulation of adenosine and 2'-deoxyadenosine, which are toxic to lymphocytes (57). Affected children are unable to generate normal immune responses and develop life-threatening infections. The normal ADA cDNA was transferred *ex vivo* with a retrovirus vector into T lymphocytes of two children with this disorder, and the modified T cells were expanded in the laboratory and periodically infused into the autologous recipients (30, 31). This resulted in an increase in

T cell numbers and in the ADA levels in circulating T cells. The two children now have partially reconstituted immune function, as demonstrated by T cell cytokine release, cytotoxic T cell activity, isohemagglutinin production, and skin test responses to common antigens. In addition, three infants with ADA deficiency who received autologous infusions of cord blood CD34⁺ stem cells modified *ex vivo* with a retrovirus vector containing the normal ADA cDNA have also shown evidence of increased numbers of blood T cells and increased ADA levels in T cells (30, 32). The results of the ADA studies are difficult to interpret, because none of these trials have been controlled and the recipients have also received the standard therapy of enzyme infusions with mono-methoxypolyethylene glycol-bovine ADA. Despite these caveats, these observations are consistent with the conclusion that this *ex vivo* gene transfer strategy evokes biologic responses that are relevant to treatment of ADA deficiency.

Familial hypercholesterolemia is a fatal disorder caused by a deficiency of LDL receptors in the liver that are secondary to mutations in the LDL receptor genes (38, 39, 58). The consequences are high levels of serum cholesterol and LDL cholesterol, premature atherosclerosis, and myocardial infarction. A retrovirus vector was used *ex vivo* to transfer the normal LDL receptor cDNA to autologous hepatocytes obtained by partial liver resection of an individual with this disorder (38, 39). After reinfusion of the modified hepatocytes into the liver

via the portal vein, there was a reduction in LDL cholesterol and in the ratio of LDL to high-density lipoprotein over 18 months, which is consistent with the concept that the corrected cells functioned *in vivo* to internalize and metabolize LDL cholesterol appropriately. Like the ADA deficiency studies, this study was partially compromised because other therapies were being administered. Furthermore, the LDL receptor gene mutations were mild and could have responded to experimental variables other than the transferred gene (58). However, similar transfer of autologous hepatocytes modified *ex vivo* to other individuals with more severe mutations of the LDL receptor gene demonstrated partial correction of a variety of lipoprotein-related metabolic parameters, which is consistent with the conclusion that this gene transfer strategy did evoke a relevant response (38).

Cystic fibrosis is the most common lethal hereditary disorder in North America (59). It is caused by mutations in the CFTR gene, a gene coding for an adenosine 3',5'-monophosphate (cAMP)-regulatable chloride channel in the apical epithelium. As a result of these mutations, the airway epithelium is deficient in CFTR function. This leads to chronic airway infection and inflammation and progressive respiratory derangement. There is compelling logic to the argument that these lung derangements could be prevented if CFTR function could be restored in these cells (60). It is difficult to assess CFTR function in the airway epithelium *in vivo* in humans, but the nasal

Table 2. Data from human gene transfer studies in which transfer of genetic material has evoked a biologic response that is relevant to the underlying disease.

Disease category	Disease	Strategy	Vector	Gene product*	Target cells	Relevant biologic response	Principal investigator	Reference number
Hereditary	ADA deficiency	<i>Ex vivo</i>	Retrovirus	ADA	Blood T cells and cord blood CD34 ⁺ stem cells	Partial restoration of immune response	Blaese, R. M.	(30-32)
	Familial hypercholesterolemia	<i>Ex vivo</i>	Retrovirus	LDLR	Hepatocytes	Partial correction of lipid abnormalities	Wilson, J. M.	(38, 39)
	Cystic fibrosis	<i>In vivo</i>	Adenovirus	CFTR	Nasal epithelium	Partial correction of potential difference abnormalities across the nasal epithelium	Welsh, M. J. Crystal, R. G.	(46, 47) (44, 62)
Acquired	Solid tumors	<i>In vivo</i>	Plasmid-liposome complex	CFTR	Nasal epithelium	Partial correction of potential difference abnormalities across the nasal epithelium	Geddes, D. M.	(51)
		<i>In vivo</i>	Plasmid-liposome complex	HLA-B7 + β_2	Tumor cells†	Specific immune response to tumor	Nable, G. J. Rubin, J. Vogelzang, N.	(52) (53, 54) (54, 55)
		<i>Ex vivo</i>	Retrovirus	IL-4	Fibroblasts‡§	Specific and nonspecific immune response to tumor	Hersh, E. Lotze, M.	(54, 56) (34)
		<i>Ex vivo</i>	Retrovirus	IL-2	Neuroblastoma‡	Specific and nonspecific immune response to tumor	Brenner, M. K.	(35)

*ADA, adenosine deaminase deficiency; LDLR, low-density lipoprotein receptor; CFTR, cystic fibrosis transmembrane conductance regulator; HLA-B7 + β_2 , histocompatibility locus antigen class I-B7 + β_2 microglobulin; IL-4, interleukin-4. †Direct administration to melanoma, colorectal carcinoma, or renal cell carcinoma. ‡Lethally irradiated, used as a "vaccine." §Combined with lethally irradiated, unmodified autologous tumor cells.

epithelium has been used as a surrogate to test the hypothesis that *in vivo* transfer of the normal CFTR cDNA will correct the functional consequences of CFTR deficiency (47, 61). The parameters measured relate to the observation that the deficiency in CFTR causes an abnormal potential difference between the nasal epithelial surface and subcutaneous tissues. Although the nasal epithelium is not identical to the airway epithelium, two of three studies with adenovirus vectors (44–47, 50, 62) and one with plasmid-liposome complexes (51) have demonstrated that *in vivo* transfer of the CFTR cDNA to the nasal epithelium evokes a partial correction of these potential difference abnormalities for 1 to 2 weeks.

There are also studies in which human gene transfer appears to have initiated biologic responses that are relevant to therapy for an acquired disorder. These are all "tumor vaccine" studies, based on the hypothesis that exaggerated local expression of an immune-related cytokine might help activate the immune system sufficiently to recognize tumor antigens and control the growth of tumor cells. In one *ex vivo* study, a retrovirus vector was used to transfer the interleukin-4 (IL-4) cDNA to autologous fibroblasts (34). The cells were then irradiated and implanted subcutaneously in the donor together with irradiated, unmodified, autologous tumor cells. In some recipients, this evoked infiltration with CD3⁺ T cells and tumor-specific CD4⁺ T cells at the immunization site, as well as enhanced expression of cell adhesion molecules on capillary endothelium. In another trial, autologous neuroblastoma cells modified *ex vivo* with a retrovirus to contain the IL-2 cDNA were lethally irradiated and implanted subcutaneously (35). In some individuals, this evoked systemic augmentation of CD16⁺ natural killer cells and tumor-specific CD8⁺ cytotoxic T cells and eosinophilia. Finally, in four trials, *in vivo* plasmid-liposome complexes were used to transfer a heterologous HLA class I-B7 cDNA and the β_2 microglobulin cDNA directly to solid tumors (52–56). In several patients, there was evidence that the gene transfer process initiated amplification of the numbers of detectable, circulating, tumor-specific cytotoxic T cells.

Insights into human biology. Experience with marking studies has shown that human gene transfer can yield important insights into human biology by making it possible to track the fate of genetically marked cells in a recipient. For example, when stored autologous marrow is used to rescue a patient from the suppression of marrow function that complicates high-dose chemotherapy for late-stage malignancy, the individual may subsequently develop a recurrence of the malignancy. Gene transfer marking

studies have helped answer the question of whether the recurrence is secondary to a residual tumor in the patient or is derived from malignant cells contaminating the reinfused banked marrow. Several studies that used an *ex vivo* strategy with a retrovirus vector to mark marrow cells with a neomycin resistance (neo^R) gene and then reinfused the marked marrow have demonstrated that contamination of the autologous marrow with malignant cells is common (11, 16–25). These observations have led to more attention being focused on purging banked autologous marrow of contaminating neoplastic cells before they are reinfused.

There are a number of strategies being developed for the use of *ex vivo* gene transfer to protect autologous T cells from infection with the HIV-1. None will work, however, if autologous T cells manipulated in the laboratory and then reinfused into an HIV⁺ individual have a short biologic half-life. The life-span of an autologous T cell in HIV⁺ individuals has been evaluated in identical twin pairs in which one twin is HIV⁺ and the other is HIV⁻ (12). A retrovirus vector was used *ex vivo* to transfer the neo^R gene into the T cells from the normal twin, and the genetically marked cells were then reinfused into the HIV⁺ twin. Some CD4⁺ and CD8⁺ marked T cells (or their progeny) survived for at least 10 months, providing a baseline to allow future studies to compare the fate of T cells that have been genetically modified to prevent HIV infection.

In a strategy to prevent reactivation of Epstein-Barr virus (EBV) and the accompanying associated lymphoproliferative disease after bone marrow transplantation, allogenic EBV-specific cytotoxic T cells (CTL) were genetically marked with a retrovirus vector, and the cells were infused into individuals at risk (15, 16). This preliminary study suggested that EBV-specific allogenic cells may help control EBV-associated complications of marrow transplantation, and the use of the marker genes demonstrated that the infused EBV-specific CTL persisted in the recipients for 10 weeks.

Two types of therapeutic studies support the biologic concept that minimal correction of a genotype can have significant phenotypic consequences. In the *ex vivo* study of retrovirus-mediated transfer of the LDL receptor cDNA into autologous hepatocytes in patients with familial hypercholesterolemia, liver biopsy several months after reinfusion of the modified hepatocytes showed that at most 5% of the total hepatocyte population expressed the normal gene *in vivo* (38, 39, 62). Despite this minimal correction, in some of the recipients there were changes in LDL-related parameters that suggested LDL receptor function in the liver had been partially restored.

Partial phenotypic correction has also been observed in most of the trials of adenovirus- and plasmid-liposome complex-mediated *in vivo* transfer of the CFTR cDNA to the nasal epithelium in CF, even though the amount of gene transfer and expression has been limited to a small fraction of the target cells (44–47, 50, 51, 62).

Finally, when adenovirus vectors are administered to experimental animals, the animals quickly develop circulating neutralizing antibodies directed against the vector (9). In two studies of administration of adenovirus vectors to the airways of individuals with CF, no circulating neutralizing antibodies were detected (44, 45, 49). This is an important observation, because the expression cassette delivered by adenovirus vectors remains epichromosomal, and thus the vector will have to be readministered as its expression wanes. Although it is possible that there are local antibodies to the vectors in these individuals (9), the lack of a systemic immune response to such an antigen load is encouraging in that it suggests that antibodies to vectors may not be a major factor limiting persistent vector expression in humans when the lung is repeatedly dosed (64).

Safety of gene transfer. The theoretical safety concerns regarding human gene transfer are not trivial. For the individual recipient, there is the possibility of vector-induced inflammation and immune responses, of complementation of replication-deficient vectors leading to overwhelming viral infection, and (for the retrovirus vectors) of insertional mutagenesis. There are also theoretical issues that are important to society, including concerns about modifying the human germ line and about protecting the environment from new infectious agents generated from gene transfer vectors carrying expression cassettes with powerful biologic functions.

There have been adverse events in the human gene transfer trials, including inflammation induced by airway administration of adenovirus vectors (44–50, 65) and by administration to the central nervous system of a xenogenic producer cell line releasing a retrovirus vector (43, 66). However, compared with the total numbers of individuals undergoing gene transfer, adverse events have been rare and have been related mostly to the dose and the manner in which the vectors were administered. Shedding of viral vectors in the *in vivo* trials was very uncommon and was limited in extent and time (42, 44–50, 65). No novel infectious agents generated from recombination of the transferred genome and the host genome or other genetic information have been detected, nor has any replication-competent virus related to the vector. Cells modified *ex vivo* with retrovirus vectors have been infused repeti-

tively without adverse effects (13, 30, 31, 35), adenovirus vectors have been administered repetitively *in vivo* to the nasal (48) and bronchial epithelium safely (64, 67), and plasmid-liposome complexes have been administered repetitively to tumors *in vivo* without complications (52–56). Finally, human gene transfer has not been implicated in initiating malignancy, although the numbers of recipients and time of observation will have to be much greater to allow definitive conclusions regarding this issue.

What Are the Obstacles to Successful Human Gene Transfer?

With the successes of the human gene transfer trials have come the sobering realities of the drug development process. Some of the problems are generic for the field, and some are specific for each vector.

Inconsistent results. All of the human gene transfer studies have been plagued by inconsistent results, the bases of which are unclear. For example, in the two children with ADA deficiency receiving intermittent infusions of autologous T cells modified *ex vivo* with the normal ADA cDNA, the resulting proportion of ADA⁺ circulating T cells has varied from 0.1 to 60% (30, 31). In the CF trials, there is evidence that adenovirus vectors and plasmid-liposome complexes can transfer the normal CFTR cDNA to the respiratory epithelium, but expression is observed in at most 5% of the target cells and is not seen in all recipients (44–51, 65). Further, an appropriate biologic response to gene transfer (correction of the abnormal potential difference across the nasal epithelium) has been observed in some patients in most, but not all, of the studies of CFTR cDNA transfer (44–47, 50, 51, 62). In most of the *ex vivo* marrow-marking trials, successful gene transfer is observed intermittently (Table 1).

Humans are not simply large mice. There have been several surprise examples, in which predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials. In tumor vaccine studies intended to evoke a tumor-directed immune response, there is no convincing evidence (other than anecdotal case reports) that tumors regress, despite the promising observations in experimental animals (34, 37, 52–56). It has also become apparent that studies in experimental animals may not necessarily predict the toxicology of vectors in humans. In one patient with CF in whom 2×10^9 plaque-forming units of an adenovirus vector containing the CFTR cDNA were administered to the lung, a transient local and systemic inflammatory syndrome was evoked, despite the fact that no clinically apparent toxicity was observed in rodents and nonhuman primates receiving

1000-fold greater doses by the same route (45). Likewise, in an *ex vivo*–*in vivo* strategy to treat glioblastoma, transfer of xenogenic retrovirus-producing cells to the tumor was accomplished without significant adverse effects in experimental animals, but the human studies have been associated with central nervous system toxicity related to transfer of the cell line to the tumor (43, 66).

Production problems. There are significant hurdles in vector production that must be overcome before large clinical trials can be initiated. Generation of replication-competent virus is observed in production of clinical-grade retrovirus and adenovirus vectors; and lack of reproducibility, aggregation, and contamination with endotoxin complicate the production of clinical-grade plasmid-liposome complexes (68).

The perfect vector. The ideal gene transfer vector would be capable of efficiently delivering an expression cassette carrying one or more genes of the size needed for the clinical application. The vector would be specific for its target, not recognized by the immune system, stable and easy to reproducibly produce, and could be purified in large quantities at high concentrations. It would not induce inflammation and would be safe for the recipient and the environment. Finally, it would express the gene (or genes) it carries for as long as required in an appropriately regulated fashion (69).

This ideal vector is conceptually impractical, because the human applications of gene transfer are broad, and the ideal vector will likely be different for each application. Clinical experience to date suggests that retrovirus, adenovirus, and plasmid-liposome vectors all need refinement, but each is relatively well suited for the clinical targets at which they have been directed. Further, the technology is now available to create designer vectors that can be optimized for each application. Among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated. Reproducible production of large amounts of pure vector is a hurdle for all classes of vectors. Some of the vector-specific hurdles are reduction of the risk for insertional mutagenesis in retrovirus vectors, minimization of the amount of immunity and inflammation evoked by the adenovirus vectors, and enhancement of the translocation of the gene to the nucleus for the plasmid-liposome complexes.

There is considerable interest in developing new vectors, but there is controversy as to which vector class is most likely to succeed, particularly for use in *in vivo* applications. There are two philosophical camps in vector design: viral and nonviral. The viral proponents believe that the most efficient

means to deliver an expression cassette *in vivo* is to package it in a replication-deficient recombinant virus. The logic supporting this approach is the knowledge that viruses are masterful at reproducing themselves, and thus have evolved strategies to efficiently express their genetic information in the cells they infect. The nonviral proponents concede this argument but believe that the redundant anti-immune and inflammatory host defenses against viruses may be a risk to recipients, will limit the duration of expression as the infected cells are recognized by the immune system, and may hinder the efficacy of repeat administration of the vectors. Thus, nonviral vector aficionados believe it is rational to start from scratch to design safe, efficient, gene transfer strategies. In contrast, the viral camp believes that it is best to start with something that works but then to circumvent the replication, immune, and inflammation risks inherent in their use by appropriate vector design. It is most likely that these philosophical differences will eventually disappear as new classes of vectors are designed that incorporate features of viral and nonviral vectors, as dictated by specific clinical applications.

Future Prospects

None of the drug development problems facing human gene transfer are insurmountable, but each will take time to solve. However, the logic underlying the potential usefulness of human gene transfer is compelling; and put in a context in which the human genome project will provide 80,000 to 100,000 human genes that could be used in expression cassettes for human gene transfer, the potential impact of this technology for innovative therapies and increased understanding of human biology is enormous.

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stitutes of Health, Suite 323, 6006 Executive Boulevard, MSC 7052, Bethesda, MD 20892-7052, USA. Human data in this review are derived from published articles and abstracts and from the December 1994 and June 1995 RAC investigator reports. Because the RAC reports are mandated, frequently updated, and public, they are an accurate gauge of the status of the field, although they are not peer-reviewed. Since the first human trial was begun in 1989, there has been an explosion of interest in human gene transfer. In the United States alone, more than 100 human gene transfer protocols have been approved by the RAC, and 637 individuals have participated in human gene transfer trials under RAC-approved protocol (summary data, RAC Report, June 1995).

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The Nematode *Caenorhabditis elegans* and Its Genome

Jonathan Hodgkin, Ronald H. A. Plasterk, Robert H. Waterston

Over the past two decades, the small soil nematode *Caenorhabditis elegans* has become established as a major model system for the study of a great variety of problems in biology and medicine. One of its most significant advantages is its simplicity, both in anatomy and in genomic organization. The entire haploid genetic content amounts to 100 million base pairs of DNA, about 1/30 the size of the human value. As a result, *C. elegans* has also provided a pilot system for the construction of physical maps of larger animal and plant genomes, and subsequently for the complete sequencing of those genomes. By mid-1995, approximately one-fifth of the complete DNA sequence of this animal had been determined. *Caenorhabditis elegans* provides a test bed not only for the development and application of mapping and sequencing technologies, but also for the interpretation and use of complete sequence information. This article reviews the progress so far toward a realizable goal—the total description of the genome of a simple animal.

Caenorhabditis elegans has many attractive features as an experimental system (1). The life cycle is simple and rapid, with a 3-day generation time, and populations can be grown with ease on agar plates or in liquid, usually by using *Escherichia coli* as a food source. These populations normally consist of only self-fertilizing hermaphrodites, but cross-fertilization is also possible, with the male sexual form. The option of reproduction by either selfing or crossing leads to very convenient genetics so that mutants can readily be generated, propagated, and

analyzed (2). A simple freezing protocol permits stable storage of all strains, which retain viability indefinitely in the frozen state.

The animal, about 1 mm long when fully grown, is completely transparent at all stages of development. Both development and anatomy are essentially invariant among wild-type individuals. At maturity, all adult hermaphrodites contain 959 somatic nuclei and fewer than 2000 germ cell nuclei. Despite its low cell number, *C. elegans* has fully differentiated tissues corresponding to those of more complicated animals. The transparency and rapid development allow direct examination of cell division and differentiation in living animals with Nomarski microscopy. The small size of the animal also permits reconstruction of the entire anatomy at the ultrastructural level with serial section electron microscopy. However, the

J. Hodgkin is in the Medical Research Council Laboratory of Molecular Biology, Cambridge, CB2 2OH, UK. R. H. A. Plasterk is in the Netherlands Cancer Institute, Division of Molecular Biology, Plesmanlaan 121, 1066 CX Amsterdam, Netherlands. R. H. Waterston is in the Department of Genetics and Genome Sequencing Center, Washington University School of Medicine, St. Louis, MO 63110, USA.

Johnson Worldwide Associates Inc.
v.
Zebco Corp.

U.S. Court of Appeals Federal Circuit

No. 98-1331

Decided April 27, 1999

United States Patents Quarterly Headnotes

PATENTS

[1] Patent construction -- Claims -- Broad or narrow (Section 125.1303)
Patent construction -- Claims -- Defining terms (Section 125.1305)

Term "heading," in claim for trolling motor autopilot device, has not been given particular meaning by patentee that limits it to direction of trolling motor itself, since many uses of term throughout patent are consistent with broader definition encompassing directions of both boat and trolling motor unit, since varied use of disputed term in written description demonstrates breadth of term, rather than providing limited definition, and since statements in prosecution history that were directed to claims not presently at issue do not limit scope of term as used in asserted claim.

PATENTS

[2] Patent construction -- Claims -- Broad or narrow (Section 125.1303)
Patent construction -- Claims -- Defining terms (Section 125.1305)

Term "coupled," in phrase "heading lock coupled to a trolling motor" found in preamble of claim for trolling motor autopilot device, has not been given particular meaning by patentee that limits it to mechanical or physical coupling, since mere inferences drawn from description of embodiment of invention cannot serve to limit claim terms, as they are insufficient to require narrower definition of disputed term, and since statements in prosecution history that were directed to claims not presently at issue do not limit scope of term as used in asserted claim.

PATENTS

[3] Patentability/Validity -- Specification -- Written description (Section 115.1103)

Asserted claim of patent for trolling motor autopilot device is not rendered invalid for violation of written description requirement of 35 U.S.C. Section 112 if claim term "heading" is construed to encompass both direction of trolling motor and direction of boat, since term is used interchangeably throughout written description to refer both to direction of trolling motor and direction of boat, and since disclosure thus provides ample support for breadth of "heading" term, and does not unambiguously limit its meaning to direction of motor.

PATENTS

[4] Patentability/Validity -- Anticipation -- Prior sale -- In general (Section 115.0707.01)
Patentability/Validity -- Specification -- Written description (Section 115.1103)

Infringement defendant has failed to show that claims of patent for trolling motor autopilot device are rendered invalid by on-sale bar of 35 U.S.C. Section 102(b) if construed broadly enough to cover accused device, since defendant's position reduces to argument that claims violate written description requirement of 35 U.S.C. Section 112, and thus are not entitled to filing date of parent application, since written description of patent provides ample support for ordinary and accustomed meaning of disputed claim terms, and since claims as properly construed are therefore entitled to benefit of parent application's filing date.

PATENTS

Particular patents -- Electrical -- Trolling motor autopilot

5,202,835, Knight, trolling motor with heading lock, summary judgment holding claim 1 literally infringed and not invalid affirmed.

*1608 Appeal from the U.S. District Court for the Western District of Wisconsin, Shabaz, C.J.

Action by Johnson Worldwide Associates Inc. against Zebco Corp. and Brunswick Corp. for patent infringement. From summary judgment of literal infringement, defendants appeal. Affirmed.

David L. De Bruin and Kimberly C. Tate, of Michael Best & Friedrich, Milwaukee, Wis., for plaintiff-appellee.

Kenneth J. Jurek and Rosanne J. Faraci, of McDermott, Will & Emery, Chicago, Ill., for defendants-appellants.

Before Mayer, chief judge, and Clevenger and Gajarsa, circuit judges.

Clevenger, J.

Zebco Corporation and Brunswick Corporation appeal a summary judgment of patent infringement granted in favor of Johnson Worldwide Associates by the United States District Court for the Western District of Wisconsin. See Johnson Worldwide Assocs., Inc. v. Zebco Corp., No. 97-C-453-S, slip op. at 19 (W.D. Wis. Apr. 2, 1998). Because the district court correctly construed the claims of the patent at issue and properly found no genuine issues of material fact regarding whether the patent was infringed, we affirm.

I

Johnson Worldwide Associates ("Johnson") is the holder of U.S. Patent No. 5,202,835 ("the '835 patent"), entitled "Trolling Motor With Heading Lock," which issued on December 15, 1992. [FN1] The '835 patent is generally directed to a steering control apparatus for small outboard motors, such as electric trolling motors. Trolling motors are an alternate propulsion source for small watercraft, generally intended for use while actively fishing--when the noise, vibration, and speed caused by larger or more powerful motors would diminish the chances of enticing fish to the proffered bait.

A

In broad terms, the invention of the '835 patent is a form of autopilot, described in the patent as a "heading lock," enabling directional control over the watercraft to be maintained without constant manipulation of trolling motor controls. The preferred embodiment of the '835 patent, as set forth in the written description and figures, employs a

compass mounted to the head of the "heading lock" unit, which monitors the direction of the thrust motor, specifically noting that the direction of the thrust motor is considered to be the same as the direction of the boat, as the trolling motor is mounted on the bow of the boat. See '835 patent, col. 4, lines 48-51. Claim 1 of the '835 patent, the only independent claim alleged to be infringed, provides as follows:

1. A heading lock coupled to a trolling motor producing a thrust disposed to pull a watercraft, said heading lock comprising:

a steering motor coupled to said trolling motor, said steering motor being disposed *1609 to affect the orientation of said trolling motor in response to input signals;

a steering circuit electrically coupled to said steering motor, said steering circuit [being] disposed to generate said input signals to said steering motor in response to heading signals; and

a heading detector electrically coupled to said steering circuit, said heading detector being disposed to transmit said heading signals to said steering circuit.

Zebco Corporation and Brunswick Corporation (collectively, "Zebco") sell a product under the trade name "AutoGuide" that maintains directional control of a trolling motor by use of a magnetometer located in a foot pedal. The foot pedal also contains the user controls. A microprocessor in the foot pedal sends steering signals to the steering motor through wires connecting the foot pedal to the trolling motor unit. The location of the magnetometer (in the foot pedal) is thus distinct from the location of the compass (fixed to the trolling motor head) depicted in the preferred embodiment of the '835 patent. Whether this fact is sufficient for Zebco to escape infringement of the '835 patent is the subject of this appeal.

B

In 1997, Johnson filed suit against Zebco, alleging, inter alia, that the AutoGuide unit infringed the claims of the '835 patent. The parties presented cross-motions for summary judgment on patent infringement in early 1998. On April 2, 1998, the district court agreed with Johnson's proffered claim construction, granted Johnson's motion for summary judgment of infringement, and denied Zebco's

motions. The court held that there was nothing in the intrinsic evidence of the '835 patent that compelled or supported the narrow construction of the disputed terms in the claims urged by Zebco, namely that the term "heading" in "heading signal" was limited to the direction of the trolling motor, and that the term "coupled" in "heading lock coupled to a trolling motor" was limited to a mechanical or physical connection. Without these limitations, on stipulated facts, the district court found that each element of the construed claim was literally present in Zebco's AutoGuide device. This appeal followed, vesting this court with jurisdiction pursuant to 28 U.S.C. Section 1295(a)(1) (1994).

II

We review the grant of a summary judgment de novo. See Conroy v. Reebok Int'l, Ltd., 14 F.3d 1570, 1575, 29 USPQ2d 1373, 1377 (Fed. Cir. 1994). In doing so, we must keep in mind that summary judgment is appropriate only if there is no genuine issue of material fact. See Fed. R. Civ. P. 56(c). To this end, the court must draw all reasonable factual inferences in favor of the nonmovant. See Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 255 (1986).

An infringement analysis is a two-step process in which the court first determines, as a matter of law, the correct claim scope, and then compares the properly-construed claim to the accused device to determine, as a matter of fact, whether all of the claim limitations are present, either literally or by a substantial equivalent, in the accused device. See Renishaw PLC v. Marposs Societa Per Azioni, 158 F.3d 1243, 1247-48, 48 USPQ2d 1117, 1120 (Fed. Cir. 1998); General Mills, Inc. v. Hunt-Wesson, Inc., 103 F.3d 978, 981, 41 USPQ2d 1440, 1442 (Fed. Cir. 1997); Young Dental Mfg. Co. v. Q3 Special Prods., Inc., 112 F.3d 1137, 1141, 42 USPQ2d 1589, 1592 (Fed. Cir. 1997). Because the relevant aspects of the accused device's structure and operation are undisputed in this case, the question of whether Zebco's AutoGuide product infringes the claims of Johnson's '835 patent turns on the interpretation of those claims. See Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1578, 37 USPQ2d 1365, 1370 (Fed. Cir. 1996) ("Where, as here, the parties do not dispute any relevant facts regarding the accused product but disagree over [claim interpretation], the question of literal infringement collapses to one of claim construction and is thus amenable to summary judgment.").

As we alluded to above, the crux of Zebco's argument is that the '835 patent covers only those trolling motor-autopilot systems that include a compass or other directional indicator physically attached to the trolling motor. Zebco arrives at this conclusion by the following route: (1) Zebco considers the "heading lock" invention of the '835 patent to be concerned only with the direction and orientation of the trolling motor rather than the boat; and (2) therefore the heading lock--which, according to claim 1, includes a heading detector "disposed to transmit . . . heading signals"--must be physically attached to the trolling motor. Because the accused AutoGuide systems undisputedly contain a directional indicator (a "heading detector") in a foot pedal--attached to the trolling motor via wires rather than mechanically--Zebco argues that Johnson's infringement claim must fail.

*1610 While Zebco recognizes that claim 1, the broadest claim at issue, does not explicitly require that the "heading detector" be mechanically coupled to the trolling motor, it nonetheless suggests that a proper interpretation of the terms "heading signal" and "coupled" in the language of claim 1 compels such a limited claim scope. In doing so, Zebco points out that Figure 1 of the '835 patent, and at least some of the language in the written description, suggest that the preferred embodiment of the invention includes a compass mechanically attached to the trolling motor. This case, then, presents the question of when it is permissible to narrow the scope of broad claim language by reference to embodiments described and depicted in the balance of the specification.

A

We begin, as with all claim interpretation analyses, with the language of the claims. See Renishaw, 158 F.3d at 1248, 48 USPQ2d at 1120; Abtox, Inc. v. Exitron Corp., 122 F.3d 1019, 1023, 43 USPQ2d 1545, 1548 (Fed. Cir. 1997); Bell Communications Research, Inc. v. Vitalink Communications Corp., 55 F.3d 615, 619-20, 34 USPQ2d 1816, 1819 (Fed. Cir. 1995). The general rule is, of course, that terms in the claim are to be given their ordinary and accustomed meaning. See Renishaw, 158 F.3d at 1249, 48 USPQ2d at 1121; York Prods., Inc. v. Central Tractor Farm & Family Ctr., 99 F.3d 1568, 1572, 40 USPQ2d 1619, 1622 (Fed. Cir. 1996). General descriptive terms will ordinarily be given their full meaning; modifiers will not be added to broad terms standing alone. See, e.g., Virginia Panel Corp. v.

MAC Panel Co., 133 F.3d 860, 865-66, 45 USPQ2d 1225, 1229 (Fed. Cir. 1997) (unmodified term "reciprocating" not limited to linear reciprocation); Bell Communications, 55 F.3d at 621-22, 34 USPQ2d at 1821 (unmodified term "associating" not limited to explicit association); Specialty Composites v. Cabot Corp., 845 F.2d 981, 987, 6 USPQ2d 1601, 1606 (Fed. Cir. 1988) (unmodified term "plasticizer" given full range of ordinary and accustomed meaning). In short, a court must presume that the terms in the claim mean what they say, and, unless otherwise compelled, give full effect to the ordinary and accustomed meaning of claim terms. See, e.g., Nike Inc. v. Wolverine World Wide, Inc., 43 F.3d 644, 646, 33 USPQ2d 1038, 1039 (Fed. Cir. 1994); E.I. Du Pont De Nemours & Co. v. Phillips Petroleum, 849 F.2d 1430, 1433, 7 USPQ2d 1129, 1131 (Fed. Cir. 1988); Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 759, 221 USPQ 473, 477 (Fed. Cir. 1984).

In order to overcome this heavy presumption in favor of the ordinary meaning of claim language, it is clear that "a party wishing to use statements in the written description to confine or otherwise affect a patent's scope must, at the very least, point to a term or terms in the claim with which to draw in those statements." Renishaw, 158 F.3d at 1248, 48 USPQ2d at 1121. That is, claim terms cannot be narrowed by reference to the written description or prosecution history unless the language of the claims invites reference to those sources. See, e.g., McCarty v. Lehigh Valley R.R., 160 U.S. 110, 116 (1895) ("[I]f we once begin to include elements not mentioned in the claim in order to limit such claim . . . , we should never know where to stop."); Renishaw, 158 F.3d at 1249, 48 USPQ2d at 1121. In other words, there must be a textual reference in the actual language of the claim with which to associate a proffered claim construction.

Our case law demonstrates two situations where a sufficient reason exists to require the entry of a definition of a claim term other than its ordinary and accustomed meaning. The first arises if the patentee has chosen to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term. See In re Paulsen, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994); Intellicall, Inc. v. Phonometrics, Inc., 952 F.2d 1384, 1387-88, 21 USPQ2d 1383, 1386 (Fed. Cir. 1992); Lear Siegler, Inc. v. Aeroquip Corp., 733 F.2d 881, 888-89, 221 USPQ 1025, 1031 (Fed. Cir. 1984). The second is where the term or terms chosen by the patentee so deprive the claim of clarity that there is no means by

which the scope of the claim may be ascertained from the language used. See Eastman Kodak Co. v. Goodyear Tire & Rubber Co., 114 F.3d 1547, 1554, 42 USPQ2d 1737, 1741 (Fed. Cir. 1997) (looking past claim language because of lack of clarity), overruled on other grounds by Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 46 USPQ2d 1169 (Fed. Cir. 1998) (en banc); J.T. Eaton & Co. v. Atlantic Paste & Glue Co., 106 F.3d 1563, 1568, 41 USPQ2d 1641, 1646 (Fed. Cir. 1997) (Because "[the disputed claim term] is a term with no previous meaning to those of ordinary skill in the prior art[,] [i]ts meaning, then, must be found [elsewhere] in the patent."); North Am. Vaccine, Inc. v. American Cyanamid Co., 7 F.3d 1571, 1576, 28 USPQ2d 1333, 1336 (Fed. Cir. 1993) (using the specification for guidance " [w]hen the *1611 meaning of a claim term is in doubt"); E.I. Du Pont De Nemours, 849 F.2d at 1433, 7 USPQ2d at 1131 (Fed. Cir. 1988) (the written description can supply understanding of unclear claim terms, but should never trump the clear meaning of claim terms). Cf. Comark Communications, Inc. v. Harris Corp., 156 F.3d 1182, 1187, 48 USPQ2d 1001, 1005 (Fed. Cir. 1998) ("In this case, the [disputed term] has a clear and well-defined meaning. This term is not so amorphous that one of skill in the art can only reconcile the claim language with the inventor's disclosure by recourse to the specification."). In these two circumstances, a term or terms used in the claim invites--or indeed, requires--reference to intrinsic, or in some cases, extrinsic, evidence, see Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1583, 39 USPQ2d 1573, 1577 (Fed. Cir. 1996) (reference to extrinsic evidence is proper when intrinsic evidence cannot resolve ambiguity in claim language), to determine the scope of the claim language.

B

Here, Zebco's primary claim interpretation argument is that the term "heading" in the phrase "heading signal" refers only to the direction of the trolling motor, thus requiring that the heading detector, "being disposed to transmit said heading signals," must be affixed to the trolling motor. Zebco, of course, recognizes that the ordinary and accustomed meaning of "heading" connotes only direction, rather than being limited to the direction of the trolling motor. Thus Zebco argues, as it must, for a more limited scope of "heading," to overcome the presumption in favor of the ordinary--and, in this case, broader--meaning.

[1] Because Zebco does not suggest that the phrase

"heading signal" lacks clarity as it is used in the claim, in order to establish a reason to import a narrow definition of the term, it must instead argue that the term "heading" has been given a particular meaning by the patentee. To this end, Zebco argues that language throughout the written description and prosecution history of the '835 patent demonstrates that "heading" in the context of the '835 patent is limited to the direction of the trolling motor. We find this unpersuasive, as did the district court. First, the written description does not describe "with reasonable clarity, deliberateness, and precision" the definition of "heading" proposed by Zebco. See In re Paulsen, 30 F.3d at 1480, 31 USPQ2d at 1674. Indeed, the many uses of the term throughout the '835 patent are consistent with a broader definition, one encompassing the directions of both the boat and the trolling motor unit. Compare, e.g., '835 patent, col. 3, lines 58-62 ("The electronic steering system of the present invention continues to monitor the current heading of the thrust motor" (emphasis added)) with '835 patent, col. 7, lines 37-39 ("Heading detector 204 continuously monitors the current heading of the boat" (emphasis added)). Varied use of a disputed term in the written description demonstrates the breadth of the term rather than providing a limited definition. See, e.g., Enercon GmbH v. International Trade Comm'n, 151 F.3d 1376, 1385, 47 USPQ2d 1725, 1731-32 (Fed. Cir. 1998) (refusing to limit a term used "interchangeably" in the written description to only one of the uses of the term). That the term "heading" is used at various points in the written description to refer to both the direction of the trolling motor and the boat is simply not "a special and particular definition created by the patent applicant," Renishaw, 158 F.3d at 1249, 48 USPQ2d at 1121, and is thus an insufficient reason to limit the scope of the term.

Contrary to Zebco's arguments, Laitram Corp. v. Morehouse Industries, Inc., 143 F.3d 1456, 46 USPQ2d 1609 (Fed. Cir. 1998), is inapposite. The court there held that a narrow interpretation of a disputed term was compelled because of statements in the written description that made clear that "the asserted claims will bear only one interpretation: that the 'driving surface' limitation is limited to flat driving surfaces," and that the " 'driving surface' limitation . . . requires flat driving surfaces." Id. at 1463, 46 USPQ2d at 1614-15 (emphasis added). Here, of course, there is no such unambiguous language in the written description; nothing suggests that "heading" is required to be the heading of the trolling motor. Cf. *id.*

Zebco also argues that the patentee ascribed a special meaning to the term "heading" in the prosecution history. See, e.g., Spectrum Int'l, Inc. v. Sterilite Corp., 164 F.3d 1372, 1378, 49 USPQ2d 1065, 1068-69 (Fed. Cir. 1998) (explicit meanings given to claim terms in order to overcome prior art will limit those terms accordingly); Southwall Techs., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1576, 34 USPQ2d 1673, 1676 (Fed. Cir. 1995); Standard Oil Co. v. American Cyanamid Co. 774 F.2d 448, 452, 227 USPQ 293, 296 (Fed. Cir. 1985). In particular, Zebco argues that the applicant's statement, in a June 17, 1992 amendment to the '586 application, that "the heading signal . . . *1612 is dependent solely on the heading of the motor, and totally independent of the orientation of the vessel" is a clear definition of "heading signal" as being limited to the direction of the thrust motor. However, Zebco overlooks the fact that the claims referred to in that passage, claims 4 and 14 of the '586 application, expressly included an additional limitation: that the compass be "in a substantially fixed relationship to said propulsion device," (claim 4) or likewise "in a predetermined relationship with said propulsion device" (claim 14). The argument referenced by Zebco was unquestionably focused on the requirement, in those claims, that the compass be attached to the trolling motor. The patentee's suggestion that, where the "substantially fixed relationship" or "in a predetermined relationship" claim limitation was present, the feedback signal (i.e., the heading signal) was dependent on the heading of the motor sheds no light on the meaning of "heading signal" in claims where that very limitation is not present. Rather, this exchange is an example of how carefully-crafted arguments in support of patentability can avoid creating ambiguous or adverse prosecution history. By stating clearly and particularly that the context of his remarks was in regards to claims 4 and 14, the applicant ensured that those of ordinary skill in the art--as well as courts, if need be--could evaluate the import and scope of his statements. Thus, because this argument was plainly limited to claims including a "fixed" or "predetermined" relationship between the compass and the trolling motor, it cannot be said to be a clear statement limiting the scope of "heading signal" in general. Zebco thus has not shown that sufficient reasons exist to import a limited definition of this term into the clear language of the claim.

We therefore agree with the district court that the ordinary and accustomed meaning of "heading signal" controls.

C

[2] Zebco's second interpretive argument is that the term "coupled" in the phrase "[a] heading lock coupled to a trolling motor" found in the preamble of claim 1 is limited to a mechanical or physical coupling. We are unpersuaded. Even assuming--as did the district court and Zebco--that the language of the preamble of claim 1 constitutes limitations on the claim rather than mere description, see Bell Communications, 55 F.3d at 620, 34 USPQ2d at 1820 (Fed. Cir. 1995) ("[W]hen the claim drafter chooses to use both the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects."), Zebco cannot demonstrate that a limitation to the broad and general term "coupled" must be read into the claim.

As with "heading signal," Zebco (a) recognizes that the unmodified term "coupled" generically describes a connection, and does not require a mechanical or physical coupling; and (b) does not suggest that "coupled," as used in the preamble, lacks clarity. Instead, Zebco points to passages of the written description implying the relationship between elements of the preferred embodiment, and argues that such language constitutes a special (and limited) definition of "coupled." For example, Zebco argues that the phrase "feedback means for providing a feedback signal to the control means, wherein the feedback signal is indicative of the direction of thrust," '825 patent, col. 2, lines 32-34, defines "coupled" to mean "mechanically coupled." However, just as the preferred embodiment itself does not limit claim terms, see Renishaw, 158 F.3d at 1248, 48 USPQ2d at 1120, mere inferences drawn from the description of an embodiment of the invention cannot serve to limit claim terms, e.g., Constant v. Advanced Micro-Devices, Inc., 848 F.2d 1560, 1571, 7 USPQ2d 1057, 1064 (Fed. Cir. 1988), as they are insufficient to require a narrower definition of a disputed term.

Zebco also identifies statements in the prosecution history which purport to indicate the true (and limited) meaning of "coupled." Specifically, Zebco points to the aforementioned June 17, 1992 amendment of the '586 application, where the applicant argued that "it is not obvious to affix a compass to a propulsion device in a matter recited by [the] claims." However, as we noted above, that statement lends no support to Zebco's position, as it was made in reference to original claims 4 and 14, each of which expressly required that the compass be

fixed to the trolling motor.

Because Zebco has not shown a sufficient reason to alter the clear meaning of the term "coupled," we agree with the district court that the term is not limited to a mechanical or physical coupling.

III

As alternatives to its claim construction arguments, Zebco next asserts that the relevant claim of the '835 patent, as construed by the district court (and now this court), *1613 violates the written description requirement of 35 U.S.C. Section 112, Para. 1, and the on-sale bar of 35 U.S.C. Section 102 (b). These arguments, however, break no new ground, as they essentially repeat Zebco's claim interpretation position that we considered and rejected above.

A

[3] According to 35 U.S.C. Section 112, Para. 1 (1994), a patent specification must contain a written description of the invention sufficient to "allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." See, e.g., Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 1479, 45 USPQ2d 1498, 1503 (Fed. Cir. 1998) (quoting In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)). Zebco argues that claim 1 of the '835 patent violates this requirement because, in its mind, the written description of the patent speaks of "heading" only in terms of the direction of the trolling motor, and that therefore any construction of "heading signal" encompassing both the direction of the trolling motor and the direction of the boat renders the patent invalid under section 112, Para. 1. E.g., Gentry Gallery, 134 F.3d at 1480, 45 USPQ2d at 1503-04 (finding that the written description did not support the breadth of the claims asserted by the patentee). As we noted above, however, the term "heading" is used interchangeably throughout the written description to refer to both the direction of the trolling motor and the direction of the boat. Compare, e.g., '835 patent, col. 3, lines 58-62 ("The electronic steering system of the present invention continues to monitor the current heading of the thrust motor" (emphasis added)) with '835 patent, col. 7, lines 37-39 ("Heading detector 204 continuously monitors the current heading of the boat" (emphasis added)). Thus, this case is unlike Gentry Gallery, in which this court's determination that the

patent disclosure did not support a broad meaning for the disputed claim terms was premised on clear statements in the written description that described the location of a claim element--the "control means"--as "the only possible location" and that variations were "outside the stated purpose of the invention." Gentry Gallery, 134 F.3d at 1479, 45 USPQ2d at 1503. Gentry Gallery, then, considers the situation where the patent's disclosure makes crystal clear that a particular (i.e., narrow) understanding of a claim term is an "essential element of [the inventor's] invention." Id., 45 USPQ2d at 1503. Here, however, the patent disclosure provides ample support for the breadth of the term "heading"; it does not "unambiguously limit []" the meaning of "heading" to the direction of the motor. Cf. id. at 1480, 45 USPQ2d at 1504. The district court did not err in ruling that the relevant claim of the '835 patent, as construed, was not invalid under 35 U.S.C. Section 112, Para. 1.

B

[4] Zebco's "on-sale bar" argument is essentially a reprise of its argument that the '835 patent is invalid under the written description requirement, and thus fares no better. Under 35 U.S.C. Section 102(b) (1994), a patent claim is invalid if the patented invention was "on-sale" or in public use in this country more than one year prior to the filing of the patent application from which the claim issued. See 35 U.S.C. Section 102(b); Pfaff v. Wells Elecs., Inc., U.S. , 119 S.Ct. 304, 307, 48 USPQ2d 1641, 1642 (1998). Zebco's on-sale bar theory is that the '835 patent claims, if construed broadly enough to cover the accused device, are directed to subject matter not disclosed in the '586 application, and thus are not eligible for the filing date accorded that application. Under 35 U.S.C. Section 120, claims are granted the benefit of the filing date of an earlier-filed application only if the earlier application provides support according to 35 U.S.C. Section 112, Para. 1 for the later claims. See 35 U.S.C. Section 120 (1994); Studiengesellschaft Kohle, m.b.H. v. Shell Oil Co., 112 F.3d 1561, 1564, 42 USPQ2d 1674, 1677 (Fed. Cir. 1997). Zebco posits that if the '835 patent is not entitled to the June 1990 filing date of the '586 application, then the invention of the '835 patent was on-sale or in public use more than one year before the July 1992 filing date of the '254 application, which matured into the '835 patent. [FN2] However, Zebco does not contend that the applicant impermissibly added new matter to the '254 application. Cf. 35 U.S.C. Section 132 (1994) ("No

amendment shall introduce new matter into the disclosure of the invention."). Further, there is no dispute that the disclosures of the '586 and '254 applications--and thus the '324 and '835 patents, respectively--are the same in all but a few respects. [FN3] Zebco's position thus reduces to the argument that the claims of the '835 *1614 patent violate the written description requirement of section 112, Para. 1. But to state the argument is to realize its objection; as we discussed above, the written description of the '835 patent provides ample support for the ordinary and accustomed meaning of the terms of the '835 claims. Thus, the '835 claims, as construed by the district court and this court, are entitled to the benefit of the filing date of the '586 application. No violation of section 102(b)'s on-sale bar has occurred.

IV

Zebco has failed to demonstrate to this court that the disputed claim terms of claim 1 of the '835 patent should be interpreted in a way other than their ordinary and accustomed meaning. Therefore, we find that the district court's claim interpretation, and the summary judgment of infringement conditioned thereon, was not erroneous. We also hold that the district court correctly determined that the relevant claim of the '835 patent, as construed, is not invalid. The judgment of the district court is affirmed.

AFFIRMED.

FN1 The '835 patent issued from U.S. Patent Application No. 920,254 ("the '254 application"), filed on July 17, 1992, which was a continuation of U.S. Patent Application No. 537,586 ("the '586 application"), filed June 14, 1990. Johnson also holds U.S. Patent No. 5,172,324 ("the '324 patent"), entitled "Electronic Steering System," which matured from the '586 application but is not at issue in this case.

FN2 Johnson does not dispute that products embodying the '835 invention were on sale more than one year prior to the filing of the '254 application in July 1992.

FN3 The titles and abstracts are different,

for example.

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